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A sarcopenia em doentes hospitalizados: estudo do impacto clínico e económico e do método antropométrico

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Tese de Doutoramento apresentada à Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto

Ana Sofia Sousa

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Sarcopenia among hospitalized patients: clinical and financial impact and anthropometric method

Ana Sofia Sousa

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Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto

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Lista de Publicações

Fazem parte desta dissertação a seguinte publicação e manuscritos submetidos para publicação:

1. **Sousa AS**, Guerra RS, Fonseca I, Pichel F, Amaral TF. Sarcopenia among hospitalized patients - A cross-sectional study. Clin Nutr. 2014; 27 (14):00313-6.doi.org/10.1016/j.clnu.2014.12.015.

2. **Sousa AS**, Guerra RS, Fonseca I, Pichel F, Amaral TF. Sarcopenia and length of hospital stay [*submitted for publication*].

3. **Sousa AS**, Guerra RS, Fonseca I, Ferreira S., Pichel F, Amaral TF. Financial impact of sarcopenia on hospitalization costs [*submitted for publication*].

4. **Sousa AS**, Fonseca I, Pichel F, Amaral TF. Effects of posture and body mass index on body girths assessment [*submitted for publication*].

5. **Sousa AS**, Fonseca I, Pichel F, Amaral TF. Triceps skinfold compressibility in hospitalized patients – an exploratory analysis [*submitted for publication*].

Colaborei na definição dos objetivos, na recolha, na análise e na interpretação dos dados de todos os manuscritos e do artigo.
Fui responsável pela redação da versão inicial de todos os manuscritos e colaborei ativamente na elaboração de todas as versões do artigo.

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Abstract

According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is a condition defined as the loss of both muscle mass and muscle function (strength or performance). Sarcopenia is a complex phenomenon and there are several factors associated with the development of this condition.

Sarcopenia is diagnosed using muscle mass, strength and physical performance data. There is lack of standardization of the diagnostic procedures, but this classification can be improved. Nevertheless, prevalence of sarcopenia varies widely depending on the methodology used for its diagnosis. Moreover, although sarcopenia is mainly considered as a geriatric syndrome, this condition has been also reported as being present in younger adults. However, the problem of sarcopenia among hospitalized younger adults remains to be documented.

Sarcopenia has been previously described as being related with poor clinical outcome in hospitalized patients. However, in regards to the association of sarcopenia with length of hospital stay, information is scarce and controversial. Moreover, data on financial burden of sarcopenia in hospital setting is limited to surgical patients.

Concerning the assessment of hospitalized patients, anthropometry provides useful information on body composition and is of utmost importance in nutrition risk screening and evaluation. Even though anthropometric measures, such as body circumferences and skinfold thickness, are not considered by the EWGSOP as being suitable for routine use in clinical practice, they still are amongst the most relevant methods for body composition assessment due to their predictive value and their practicability. Therefore, reducing potential sources of error in body

circumferences and skinfold thickness assessment would be advantageous in order to provide a more valid and broader use of anthropometry.

The present thesis aims to evaluate the frequency of sarcopenia among hospitalized patients and to study the impact of different diagnostic criteria on sarcopenia diagnosis (paper 1). It also aimed to identify factors associated with sarcopenia and to increase the knowledge about clinical (paper 2) and financial impact (paper 3) of sarcopenia among hospitalized patients. Furthermore, the present work aimed to explore potential sources of error in the assessment of body circumferences (paper 4) and skinfold thickness (paper 5).

The first three studies that compose the present thesis were conducted among a consecutive sample of respectively 608, 655 and 656 hospitalized patients aged ≥18 years. Studies 4 and 5 were conducted among a convenience sample of 123 and 106 patients, respectively. The design of studies 1, 4 and 5 is cross-sectional, while studies 2 and 3 are prospective.

Paper 1 results showed that 25.3% patients were sarcopenic. However, depending on age and on the applied criteria, frequency of sarcopenia varied from 5% to 41.1% for men and from 4.9% to 38.3% for women. There was 95.7% (k = 0.89) agreement between criteria that estimated muscle mass by bioelectrical impedance analysis. According to the EWGSOP criteria, approximately 20% of the non-undernourished patients were sarcopenic and 29.5% of the overweight and 18.7% of the obese patients were also sarcopenic. Furthermore, 19.8% patients aged 18 to 64 years were sarcopenic.

Factors associated with sarcopenia (Paper 2) were male gender, age ≥65 years, moderate or severe dependence, undernutrition and being admitted to a medical ward. Sarcopenic patients presented a lower probability of being discharged home (Hazard Ratio (HR), 95% Confidence Interval (CI) = 0.71, 0.58-0.86). However, after stratifying for age groups, this effect was visible only in patients aged <65 years (HR, 95% CI= 0.66, 0.51-0.86). Moreover, sarcopenic overweight or obese patients presented a higher probability of being discharged home (HR, 95% CI = 0.78, 0.61-0.99) than non-overweight sarcopenic patients (HR, 95% CI = 0.63, 0.48-0-83).

Paper 3 showed that sarcopenia independently increased hospitalization costs by €1240 (95 % CI: €596-1887) for patients aged <65 years and €721 (95% CI: €13-1429) for patients aged ≥65 years. Sarcopenic overweight was also independently related to an increase in hospitalization costs of €884 (95% CI: €295-1476).

Regarding the effects of posture and body mass index on body girths assessment (paper 4), body girths obtained in the supine and standing positions were compared according to body mass index (BMI) normal weight and overweight categories. Significant differences were found between measurements obtained in standing and supine positions, ranging from 0.6 to 1.1 cm. Intraclass correlation coefficient values were ≥0.97 and agreement ranged from 81.3% to 87% (weighted k ≥0.84). Similar results were found when differences were stratified by BMI categories.

The aim of paper 5 was to explore and describe, through an innovative technique, triceps skinfold (TSF) compressibility and its associated factors among a sample of hospitalized patients. Compressibility was determined according to a definition based on a measurement of time (τ) that reflects adipose tissue dynamic response to compression, and it was also defined according to the difference between the initial and final TSF value (TSF difference). Results from multivariable linear regression models showed that time of compressibility (τ) was not significantly associated with any of the included variables, but compressibility based on difference of TSF values was independently associated with TSF thickness (regression coefficient (95% Confidence Interval) = 0.38 (0.01-0.05), *p*=0.002) and with nutritional status (regression coefficient (95% Confidence Interval) = 0.23 (0.12-1.23), *p*=0.018).

The present work results lead to the following conclusions: (1) sarcopenia is frequent among hospitalized patients and this frequency varies widely depending on the applied diagnostic criteria; sarcopenia was identified in a considerable proportion of adult patients aged between 18 and 64 years and in those who were non-undernourished, namely among overweight and obese; (2) being male, aged ≥65 years, being dependent, being undernourished and being admitted to a medical ward were factors associated with sarcopenia among hospitalized adult patients; sarcopenia is independently associated with longer LOS, although this association is stronger for patients aged 18 to 64 years; moreover, sarcopenic overweight was associated with a higher probability of discharge home than non-overweight sarcopenia; (3) sarcopenia is independently associated with hospitalization costs, increasing hospitalization costs in 52.7% (58.5% for patients aged < 65 years and 34% for patients aged ≥ 65 years); (4) body girths assessment in standing and supine positions in hospitalized adults and older adults differ. However, these differences are small and they are not dependent on BMI categories; (5) among a sample of hospitalized patients, time of compressibility (τ) was not related with any of the studied factors. However, undernutrition risk and the TSF thickness were factors independently associated with higher compressibility assessed by the difference between the initial and final TSF value. Although this is an exploratory attempt to describe compressibility and its associated factors, our results emphasize the need for further research in order to determine the most accurate method to quantify compressibility, to infer on the associated factors and to control its effect.

The present work results increased the knowledge on the burden and on the diagnostic criteria of sarcopenia in a clinical perspective and demonstrated that this condition is not merely a geriatric syndrome on a hospital setting. Moreover, the recognition of small posture and physical complexion related errors associated to body girths assessment and the advancement in the possibility to quantify skinfolds compressibility may be useful insights concerning the use of anthropometric measures.

Resumo

O *European Working Group on Sarcopenia in Older People* (EWGSOP) define a sarcopenia como a perda de massa e de função muscular (força ou desempenho). A sarcopenia é um fenómeno complexo e existem diversos fatores associados ao desenvolvimento desta condição.

O diagnóstico da sarcopenia é realizado através da avaliação da massa e da força muscular e do desempenho físico. Não existem procedimentos de diagnóstico padronizados, mas este processo poderá ser otimizado. Todavia, a prevalência da sarcopenia apresenta grande variação, dependendo do método seguido para o seu diagnóstico. Para além disso, embora a sarcopenia seja geralmente considerada uma síndrome geriátrica, esta condição foi já descrita como estando presente em adultos mais jovens. Contudo, o problema da sarcopenia em adultos jovens hospitalizados não foi ainda documentado.

A sarcopenia foi anteriormente relacionada com pior prognóstico em doentes hospitalizados. Porém, relativamente à associação da sarcopenia com o tempo de internamento, a informação atualmente existente é escassa e controversa. Além disso, a informação sobre o impacto económico da sarcopenia em contexto hospitalar é limitada a doentes cirúrgicos.

Relativamente à avaliação de doentes hospitalizados, a antropometria fornece informação de grande utilidade sobre a composição corporal e é da maior importância no rastreio do risco nutricional e na avaliação do estado nutricional. Embora as medições antropométricas, como os perímetros corporais e as pregas

cutâneas, não sejam consideradas pelo EWGSOP como adequadas para utilização por rotina na prática clínica no diagnóstico da sarcopenia, estão entre os métodos mais relevantes para a avaliação da composição corporal, devido ao seu valor preditivo e fácil aplicabilidade. Assim, a redução de potenciais fontes de erro na avaliação de perímetros corporais e de pregas cutâneas, poderá ser vantajosa, uma vez que poderá permitir melhorar a validade da antropometria.

A presente tese tem como objetivo avaliar a frequência da sarcopenia e estudar o impacto de diferentes critérios de diagnóstico (artigo 1). Este trabalho teve também como objetivo identificar os fatores associados com a sarcopenia e aumentar o conhecimento acerca do seu impacto clínico (artigo 2) e económico (artigo 3) em doentes hospitalizados. Foram ainda objetivos deste trabalho explorar potenciais fontes de erro na avaliação de perímetros corporais (artigo 4) e de pregas cutâneas (artigo 5).

Os primeiros três estudos que compõem esta tese foram conduzidos numa amostra consecutiva de, respetivamente, 608, 655 e 656 doentes hospitalizados com idade igual ou superior a 18 anos. Os estudos 4 e 5 foram conduzidos numa amostra de conveniência de 123 e 106 doentes, respetivamente. Os estudos 1,4 e 5 são transversais, enquanto os estudos 2 e 3 são prospetivos.

Os resultados do artigo 1 mostram que 25,3% dos doentes avaliados encontravam-se sarcopénicos. No entanto, dependendo da idade e do critério aplicado, a frequência da sarcopenia variou de 5% a 41,1% nos homens e de 4,9% a 38,3% nas mulheres. Encontrou-se uma concordância de 95,7% (k = 0,89) entre os critérios que estimaram a massa muscular através de impedância bioelétrica.

De acordo com os critérios do EWGSOP, aproximadamente 20% dos doentes não desnutridos encontravam-se sarcopénicos e 29,5% dos doentes com excesso de peso e 18,7 % dos doentes obesos estavam também sarcopénicos. Além disso, 19,8% dos doentes com idade compreendida entre os 18 e os 64 anos encontravam-se sarcopénicos.

Os fatores associados com a presença de sarcopenia (artigo 2) são o sexo masculino, idade igual ou superior a 65 anos, dependência moderada ou grave, desnutrição e admissão hospitalar num serviço médico. Os doentes sarcopénicos apresentam menor probabilidade de ter alta do hospital (*Hazard Ratio* (HR); Intervalo de Confiança (IC) 95% = 0,71; 0,58-0,86). No entanto, após estratificação por grupos etários, este efeito foi visível apenas nos doentes com idade compreendida entre os 18 e os 64 anos (HR; IC 95% = 0,66; 0,51-0,86). Além disso, doentes com excesso de peso sarcopénico ou obesidade sarcopénica apresentaram maior probabilidade de ter alta (HR; IC 95%= 0,78; 0,61-0,99) do que os doentes sarcopénicos sem excesso de peso ou obesidade (HR; IC 95% = 0,63; 0,48-0,83).

O artigo 3 mostra que a sarcopenia aumenta de forma independente os custos de hospitalização em €1240 (IC 95%: €596-1887) nos doentes com idade compreendida entre 18 e 64 anos e em €721 (IC 95%: €13-1429) nos doentes com 65 ou mais anos. O excesso de peso sarcopénico associou-se a um aumento independente de €884 (IC 95%: €295-1476) dos custos de hospitalização.

Quanto aos efeitos da postura e do índice de massa corporal (IMC) na avaliação de perímetros corporais (artigo 4), os perímetros corporais obtidos na posição ortostática e em decúbito dorsal foram comparados de acordo com duas categorias de IMC: peso normal e excesso de peso ou obesidade. Encontraram-se diferenças significativas entre 0,6 e 1,1 cm, entre as medições obtidas em posição ortostática e em decúbito dorsal. Os valores dos coeficientes de correlação intraclasse foram ≥0,97 e a concordância variou de 81,3% a 87% (k ponderado ≥0,84). Obtiveram-se resultados semelhantes quando as diferenças foram estratificadas por categorias de IMC.

Com o artigo 5 pretendeu-se explorar e descrever, através de uma técnica recentemente desenvolvida, a compressibilidade da prega cutânea tricipital (PCT) e os seus fatores associados numa amostra de doentes hospitalizados. A compressibilidade foi determinada de acordo com uma definição baseada numa medida de tempo (τ) que reflete a resposta dinâmica do tecido adiposo à compressão, e foi também definida de acordo com a diferença entre o valor inicial e o valor final da PCT (diferença de PCT). Resultados provenientes de modelos de regressão linear mostraram que o tempo de compressibilidade (τ) não se encontra significativamente associado com nenhuma das variáveis incluídas. Contudo, a compressibilidade baseada na diferença de valores da PCT encontra-se independentemente associada com a espessura da PCT (coeficiente de regressão (intervalo de confiança a 95%) = 0,38 (0,01-0,05), *p*=0,002) e com o estado nutricional (coeficiente de regressão (intervalo de confiança a 95%) = 0,23 (0,12-1,23), *p*=0,018).

Os resultados do presente trabalho conduzem às seguintes conclusões: (1) a sarcopenia é frequente em doentes hospitalizados e esta frequência apresenta grande variação, dependendo do critério de diagnóstico aplicado; identificou-se a sarcopenia numa proporção considerável de doentes adultos com idade compreendida entre os 18 e os 64 anos e também em doentes não desnutridos, com excesso de peso e em obesos; (2) ser do sexo masculino, com idade igual ou superior a 65 anos, apresentar dependência, estar desnutrido e ser hospitalizado num serviço médico são fatores associados à presença de sarcopenia em doentes adultos hospitalizados; a sarcopenia encontra-se independentemente associada a maior tempo de internamento, embora esta associação seja mais forte em doentes com idade compreendida entre os 18 e os 64 anos; o excesso de peso sarcopénico relaciona-se com maior probabilidade de ter alta do que a sarcopenia não associada com excesso de peso; (3) a sarcopenia associa-se de forma independente com os custos de hospitalização, aumentando-os em 52,7% (58,5% em doentes com idade inferior a 65 anos e 34% em doentes com 65 ou mais anos); (4) a avaliação de perímetros corporais em posição ortostática e em decúbito dorsal em doentes hospitalizados difere mas estas diferenças são pequenas e não dependem das categorias de IMC; (5) numa amostra de doentes hospitalizados, o tempo de compressibilidade (τ) não se encontrava associado com nenhum dos fatores estudados. No entanto, o risco de desnutrição e a espessura da PCT são fatores independentemente associados com um aumento da compressibilidade, definida como a diferença entre o valor inicial e o valor final de PCT. Embora se trate de uma análise exploratória para descrever a compressibilidade e os seus efeitos, estes resultados realçam a necessidade de mais investigação de forma a determinar o método mais preciso para quantificar a compressibilidade, para inferir sobre os fatores associados e controlar o seu efeito.

Os resultados da presente tese aumentaram o conhecimento acerca do problema e dos critérios de diagnóstico da sarcopenia numa perspetiva clínica e demonstraram que esta condição não é meramente uma síndrome geriátrica em contexto hospitalar. Além disso, o reconhecimento dos pequenos erros associados à postura e à compleição física na avaliação de perímetros corporais e o avanço na possibilidade de quantificar a compressibilidade de pregas cutâneas poderão ser indicações úteis no que concerne à utilização de medições antropométricas.

Index

Abbreviations

BIA, bioelectrical impedance analysis

BMI, body mass index

EWGSOP, European Working Group on Sarcopenia in Older People

HGS, handgrip strength

LOS, length of hospital stay

MAMC, mid-arm muscle circumference

NRS-2002, Nutritional Risk Screening

PG-SGA, Patient-Generated Subjective Global Assessment

TSF, triceps skinfold

WHO, World Health Organization

Introduction

Introduction

1. Sarcopenia

1.1. Definition: definition and diagnosis

The term "sarcopenia" (from the Greek, *sarx*, flesh and *penia*, loss) was firstly proposed by Irwin Rosenberg in 1989 [(1)] in order to describe age-related decline of muscle mass. Since then, muscle strength has been added as a possible diagnostic parameter [(2)]. However, a widely accepted definition of sarcopenia suitable for use in both research and clinical practice was still lacking.

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) [(3)] proposed a definition of sarcopenia recommending the use of the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia. Thus, according to this consensus, diagnosis of sarcopenia requires the documentation of low muscle mass plus documentation of either low muscle strength or low physical performance [(3)].

Muscle strength was found to be relevant as a novel sarcopenia diagnosis parameter because it does not depend merely on muscle mass [(4)] and, consequently, the diagnosis of sarcopenia based on muscle mass could be of limited clinical value [(3)]. Therefore, an operational definition with consensus diagnostic criteria for sarcopenia was reported by the EWGSOP, which provided a working definition of sarcopenia as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with risk of adverse outcomes such as physical disability, poor quality of life and death" [3]. Previously, in 2009, there was a similar but more restricted approach, released by the International Working Group on Sarcopenia [5], who provided a definition of sarcopenia as "age-associated loss of skeletal muscle mass and function", with the diagnosis based on a low whole-body or appendicular fat-free mass in combination with poor physical function.

1.2. Prevalence

Sarcopenia is estimated to occur in between 1 to 29% of community dwelling older adults and 14 to 33% of older adults in long-term care [6]. There is less evidence regarding the prevalence of sarcopenia in the hospital setting. However, the available information suggests a prevalence of sarcopenia among hospitalized older patients ranging from 10 to 25.3% [7-10], as these values depend on the diagnostic criteria and methodology used in the different studies.

Moreover, although sarcopenia is mainly associated with older ages and is considered as a geriatric syndrome, this condition can also be present in younger adults, especially when associated with illnesses such as dementia and osteoporosis [3]. A study from 2013 [11] reported the presence of sarcopenia among healthy community dwelling individuals aged over 45 years, describing a prevalence of 9% in the individuals aged between 45 and 54 years and 13.5% in those aged 55 to 64 years. Nevertheless, the burden of sarcopenia among hospitalized younger adults remains to be documented.

1.3. Etiology

There are several factors associated with the development of sarcopenia as this condition is a complex phenomenon [3, 5, 12]. The main causes include genetic heritability [13-15], nutritional status (low protein intake, low energy intake and low vitamin D status) [16-21], low physical activity [22-25], hormonal changes, namely a decline in serum testosterone and growth hormone [26, 27], insulin resistance [28-30], atherosclerosis [31-33] and changes in circulating pro-inflammatory cytokines [34].

Figure 1 summarizes factors which have been associated with the etiology of sarcopenia.

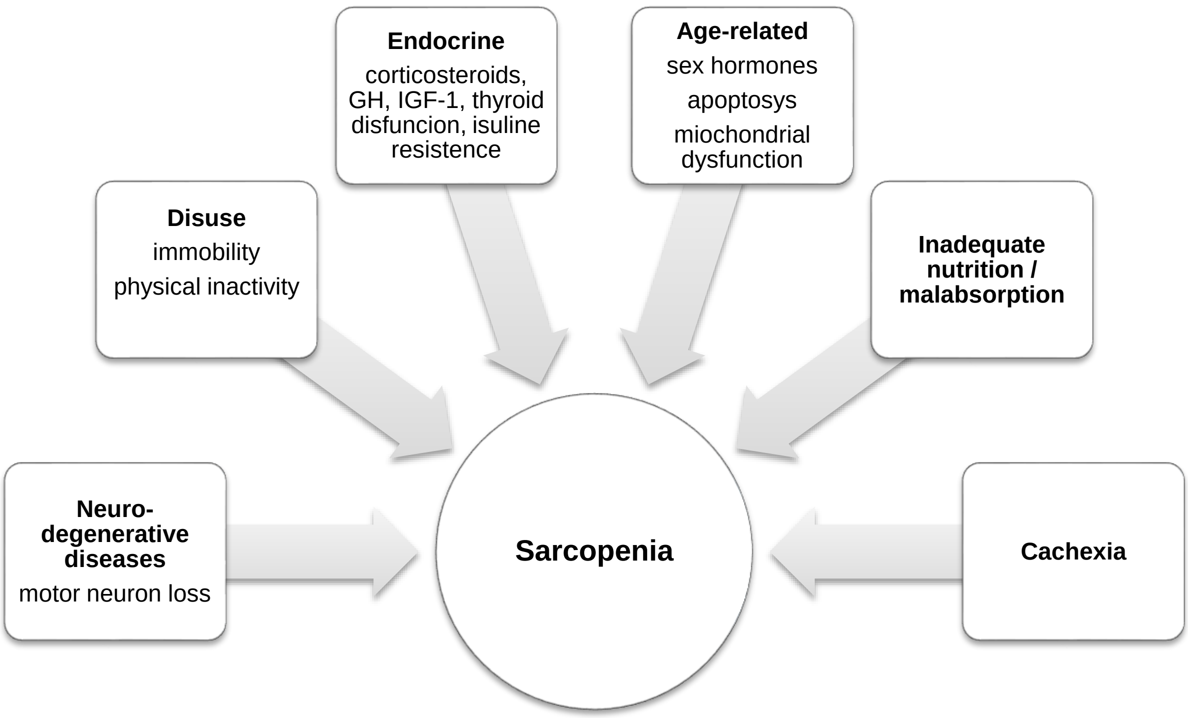

Figure 1 – Mechanisms of sarcopenia. Adapted from: Cruz-Jentoft *et al*. Age and Ageing 2010; 39: 412–423.

As sarcopenia presents different possible causes, the theoretical categorization may be useful for clinical practice [(3)]. Therefore, according to the consensus from the EWGSOP [(3)], sarcopenia can be categorized into primary, or age-related, when there is no other evident cause but ageing and secondary, when one or more causes can be identified. Thus, besides primary or age related, sarcopenia can also be activity related (ex: bed rest), disease related (ex: organ failure, inflammatory disease) or nutrition related (ex: malabsorption).

The conceptual stages of sarcopenia were also described in order to facilitate clinical approach [(3)]. As a result, an individual can be presarcopenic, sarcopenic or severely sarcopenic, depending on the severity of the condition. Table 1 summarizes this categorization.

Stage	Muscle Mass	Muscle strength		Performance
Presarcopenia	↓			
Sarcopenia	↓	↓	Or	↓
Severe sarcopenia	↓	↓		↓

Table 1 – Conceptual stages of sarcopenia. Adapted from: Cruz-Jentoft *et al.* Age and Ageing 2010; 39: 412–423.

1.3.1. Sarcopenia *versus* cachexia

Cachexia is a complex metabolic syndrome associated with an underlying disease (35), such as cancer, congestive cardiomyopathy and end-stage renal disease (36). Moreover, the loss of muscle mass, with or without loss of fat mass, is related to this condition (35). Cachexia is often associated with inflammation, insulin resistance, anorexia, and increased protein catabolism (37).

Inflammation is, therefore, the key factor, and weight loss is the main symptom. Most cachectic individuals are also sarcopenic (38). However, not all sarcopenic individuals could be considered cachectic. Cachexia occurs in individuals of any age and it is considered as an accelerated primary model of sarcopenia (39).

In a clinical perspective, it is important to distinguish sarcopenia from cachexia and starvation, because all these conditions cause loss of skeletal muscle mass and strength (40), however starvation readily reacts to nutrition support, whereas cachexia and sarcopenia can be refractory to nutritional interventions (36)..

1.3.2. Sarcopenia *versus* frailty

Frailty is defined as a geriatric syndrome resulting from cumulative declines across multiple systems and is associated with impaired homeostatic reserve and a reduced ability to withstand stress (41, 42). Therefore, this condition is related to increasing vulnerability to adverse outcomes such as falls and mortality (41, 42).

Unintended weight loss, exhaustion, weakness, slow gait speed and low physical activity are the features that support a frailty diagnosis [42].

Frailty and sarcopenia overlap as most frail older individuals are sarcopenic, and there are older people with sarcopenia who are also frail [3]. Notwithstanding this, the concept of frailty goes beyond physical factors and includes also psychological and social dimensions such as cognitive status, social support and other environmental factors [41].

1.3.3. Sarcopenic obesity

The co-occurrence of sarcopenia with increased fat mass is defined as sarcopenic obesity, which may carry the cumulative risk derived from each of the two conditions [43, 44]. Excess adiposity on its own may generate significant adverse health effects such as hypertension, dyslipidaemia and insulin resistance and there is increasing evidence showing that these risks can be elevated by the addition of low muscle mass [45].

Sarcopenic obesity is often observed in malignancy, rheumatoid arthritis and ageing as in this conditions lean body mass is lost while fat mass may be preserved or even increased [46]. Sarcopenic obesity has been associated with aggravation on mobility dysfunction, higher dependence in activities of daily living among community dwelling individuals and with higher risk of co-morbidities in hospitalized patients [45]. The association between age-related reduction of muscle mass and strength is, in most cases, independent of body mass [47]. It had long been described that age-related loss of weight, along with muscle mass, was the main responsible for muscle weakness in older individuals [47]. However, it is now clear that muscle composition has influence on muscle quality and function, as the infiltration of fat into muscle, also known as “marbling”, lowers its quality and performance [48].

1.3.4. Sarcopenia and associated factors

Several factors have been described to be associated with the presence of sarcopenia among hospitalized and also community dwelling older adults older adults, such as age [49], schooling years [50], smoking [49] and physical activity [11], BMI [11], hormonal factors [50] and hospitalization at a medical ward. Notwithstanding this, according to current knowledge, data on factors associated with sarcopenia among hospitalized younger patients, aged 18 to 64 years, are non-existent and remain to be documented. The research for factors associated with the presence of sarcopenia is of major importance, as it may allow for the recognition of modifiable risk factors. Since modifiable factors are identified, it will be possible to act on prevention.

1.4. Diagnosis

1.4.1. Methodology

Muscle mass, strength and physical performance are the variables to assess in order to identify sarcopenia according to the EWGSOP [3]. It is important to use the most accurate method to evaluate these variables. However, the EWGSOP [3] proposes different possible techniques, considering their characteristics and suitability for use either in research or clinical practice.

For muscle mass assessment, imaging techniques, such as computed tomography (CT) scans and magnetic resonance imaging (MRI), are very precise and are able to distinguish fat from other soft tissues, features that make these methods gold standards for estimating muscle mass [3]. However, high financial costs and radiation exposure limits the use of these whole-body imaging methods in clinical practice [51]. Dual energy X-ray absorptiometry (DXA) is considered the preferred alternative method for research and clinical practice. Nevertheless, lack of portability may be a limitation for clinical use [51].

Bioelectrical impedance analysis (BIA) is an economic, easy to use, reproducible technique which used under standard conditions have been found to correlate well with MRI predictions [52]. Therefore, this technique is considered a valid alternative to DXA [3].

Other muscle mass estimation methods include anthropometric measures such as mid-arm circumference and skinfold thickness. However, changes in adiposity that occur with ageing and the decline of skin elasticity contribute to errors of estimation in older people, making anthropometric measures vulnerable to error [53]. The EWGSOP does not recommend anthropometry for routine use in the diagnosis of sarcopenia [3].

Considering muscle strength evaluation, handgrip strength is considered the best and most suitable technique. This measurement has been strongly associated with lower extremity muscle power, knee extension, calf cross-sectional muscle area and is also a clinical marker of mobility [54].

For physical performance, the Short Physical Performance Battery (SPPB), a combined method for assessing physical performance is referred as a standard measure [3]. This method evaluates balance, gait speed, strength and endurance [55]. Gait speed, which is a part of the SPPB, can also be applied as a single test [3]. Timed get-up-and-go (TGUG) test which measures the time needed to complete a series of functional task and evaluates balance is another possible examination of performance [56, 57].

1.4.2. Definition of cut-offs for diagnostic measurements

Cut-off points depend on the selected technique and the lack of reference studies limits value standardization. Therefore, the European consensus proposes various cut-off points for each recommended method or technique based on the information available, considering the assessment of muscle mass using DXA and BIA, muscle strength (by handgrip strength) or physical performance, assessed by SPPB or gait speed [3].

Despite the EWGSOP [3] recommendations concerning the most suitable methods and cut-off points, there is lack of standardization of the diagnostic procedures. Thus, prevalence of sarcopenia varies widely depending on the methodology used to diagnose this condition [58, 59].

1.5. Sarcopenia amongst hospitalized patients

1.5.1. Clinical impact

Sarcopenia has been previously described as being related with poor clinical outcome in hospitalized patients. This condition has also been associated with higher mortality [7, 60], higher risk of non-elective readmission in a six month period [7] and worst post-operative outcomes [61-65].

Length of hospital stay (LOS) is a widely used indicator of the changes that occur during a hospitalization process and can be used as a surrogate marker of health status [66]. Thus, prediction of LOS may lead to a maximization of resources [67].

Concerning the association of sarcopenia with LOS, information is scarce and controversial. Results from a study conducted among hospitalized patients aged ≥65 years showed that sarcopenic patients with a mean age of 79 years had longer LOS than non-sarcopenic patients [7]. In contrast, no differences in LOS between sarcopenic and non-sarcopenic older patients with a mean age of 84.2 years were reported by Cerri *et al.* [9]. Moreover, a study conducted among cancer patients, with sarcopenia defined through computed tomography scans, reported sarcopenic patients to present longer LOS than non-sarcopenic patients (39 days *versus* 30 days, $p<0.001$) [61].

The establishment of an association between sarcopenia and LOS is, therefore, of utmost importance in order to provide a more effective healthcare plan and reduce adverse consequences.

The potential effect of confounding factors on the association between sarcopenia and LOS remains to be described, as well as the quantification of the association of sarcopenia with LOS among a wide-ranging sample of hospitalized patients. Increasing the knowledge on this subject could be a major advantage for clinical setting, in order to provide a more effective healthcare plan and thus reducing the adverse consequences that sarcopenia entails.

1.5.2. Financial impact

Considering the previously described impact of sarcopenia on hospitalized individuals, healthcare costs of this condition are expected to be high [68]. Notwithstanding this, data on the financial burden of sarcopenia are limited. One study from 2004 [69], which was conducted among representative samples of American adults aged ≥ 60 years, reported that the estimated healthcare cost attributable to sarcopenia defined merely as the loss of muscle mass was $18.5 billion, being $10.8 billion in men and $7.7 billion in women. Nevertheless, although sarcopenia has been previously associated to higher hospitalization costs, this information is still limited to surgical patients [70-72]. Thus, the impact of sarcopenia on hospitalization costs among a wider group of patients remains to be documented.

Considering the adverse consequences sarcopenia entails among hospitalized patients and the financial constraints that healthcare systems often face, in order to maximize resources and provide a more effective healthcare plan, it is important to recognize and to explore the association of sarcopenia with hospitalization costs.

2. Anthropometry and body composition assessment

Anthropometry, from the Greek *anthropos*, man, and *metron*, measure, is defined as a measure to study human body dimensions and has been used since ancient times [73, 74]. This method was originally used, not for science but for artistic purpose: painters and sculptors needed information about human body constitution so that they could make authentic representations [75].

Anthropometry was firstly applied for epidemiological studies, specifically for nutritional assessment and its association with clinical outcomes, in the second half of the twentieth century [76]. Anthropometric measures provide useful information on body composition assessment and the techniques used are non-invasive, economic and easy-to-use both for clinical practice and research purposes [77-79].

These measures are of utmost importance in nutrition risk screening and assessment, particularly in hospital settings, as undernutrition is an important predictor of poor prognosis and longer length of hospital stay [80, 81].

Anthropometric measures are not currently recommended by the EWGSOP as a method for sarcopenia diagnosis. However, as mentioned above, besides being universally used, anthropometry is often the only available method for professionals to evaluate body composition and nutrition status in clinical settings. Therefore, even though anthropometric measures are not considered by this European Consensus as being suitable for routine use in clinical practice, they still are amongst the most relevant methods for body composition assessment. Thus, concerning the identification of sarcopenia, anthropometric measurements can still be applied for screening purposes and, therefore, be used as complimentary methods to the recommended techniques.

Body circumferences and skinfold thickness are amongst the most widely used measures, both for research and clinical practice, due to their predictive value and association with a variety of conditions, in addition to their usefulness for predicting other relevant anthropometric measurements, such as weight and height when their measurement is impossible to obtain.

2.1. Assessment of body circumferences: the effect of posture and body complexion

For the assessment of body circumferences, protocols currently used [82] indicate supine position as the correct position for performing measurements. However, especially in hospital settings, individuals are often unable to change their body position [83, 84]. For instance, to evaluate a critical patient or a bedridden patient, it is necessary to adapt the standard procedure to the body position.

Body circumference results, namely arm, waist, hip and calf girths, are frequently used for body composition and nutritional assessment purposes, isolated or as part of undernutrition diagnosis and screening tools [85, 86]. The effect of posture on body circumferences assessment could be of major relevance as it can compromise the entire body composition assessment results.

Previous reports had shown that body posture influenced anthropometric measurements of the lower limbs in young free-living adults [83] and, more recently, a study conducted among institutionalized and hospitalized older adults aged ≥65 years [87] showed that differences between body circumferences measurements obtained on standing and supine positions did not have clinically relevant impact on nutritional assessment. However, it is not known if age-related differences in body composition can change these results when younger hospitalized individuals are assessed. Nevertheless, information on the effect of posture on body circumferences in hospitalized younger adult patients aged < 65 years, is still lacking.

Besides posture, factors such as physical complexion are also susceptible of introducing bias in body circumferences assessment. Anthropometric measurements in obese (or overweight) patients, due to the presence of a larger body size are more susceptible to error, even with a trained anthropometrist. Thus, it not currently known if posture related changes differ when measurements are evaluated in overweight or obese subjects rather than in individuals with normal weight. This possible influence of overweight or obesity in body circumferences assessment needs to be documented, as, in clinical practice, this effect can lead to a misinterpretation of anthropometry and, consequently, a misclassification of nutritional status assessment.

2.2. Skinfold thickness measurement: the effect of compressibility

Skinfold thickness data allows for inference on body composition [88]. This is a substantially used measurement for monitoring subcutaneous adiposity due to its accessibility and non-invasive nature [89]. Moreover, this measurement can be used to predict adiposity and it is integrated, along with mid-arm circumference, in mid-arm muscle circumference formula, through which it is possible to estimate muscle mass [76].

In skinfold thickness measurement using a skinfold calliper, a constant pressure is applied for two seconds [82]. Tissue's dynamic response to this pressure is defined as compressibility and it has been studied using coarse methods based on the comparison between skinfold calliper measurements and subcutaneous fat thickness assessed by imaging methods or cadaver studies [88, 90].

Moreover, there are assumptions that underlie the estimation of body fatness, based on skinfold thickness measure: skin thickness is negligible, adipose tissue has constant characteristics and also that proportion of subcutaneous to visceral fat is equivalent in all subjects [88]. However, based on the previous studies using empiric comparisons and cadaver studies [89-91], it has been shown that compressibility varies according to the body part where measurement is performed and also between individuals.

Some individual characteristics have been described as being associated with compressibility, namely the site of measurement [92], gender [90], age [93], skin thickness [94], hydration status [93] and subcutaneous tissue pressure [94]. This variability affects the relation between the measurement and the actual adipose thickness, introducing error in the estimation of body fatness [88, 90]. Over the past few years, knowledge on compressibility has not significantly increased and up-to-date information on this subject is scarce.

Recently, a new skinfold calliper was developed, the Lipotool® (Fig.2) [95]. This calliper is automatic and acquires sixty measurements per second, firstly allowing for documenting tissue's dynamic response to a constant pressure of 10 g/mm^2. Thus, it will firstly enable to identify factors related to skinfold compressibility [95].

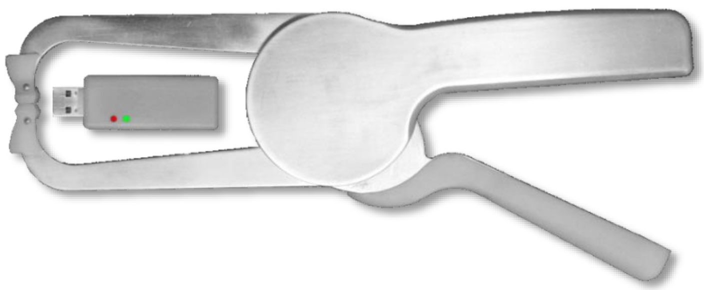

Figure 2 – Lipotool® skinfold calliper

Considering the wide use of skinfold thickness, the recognition of skinfold thickness compressibility is of utmost importance, as it may allow to control for the differences of the compressibility on the measurements and its interpretation. Thus, reducing bias would be advantageous in order to provide a more valid use of anthropometry.

Aims

Aims

The present work aims to:

1. Increase the knowledge about sarcopenia among hospitalized patients (Chapter I)
    1.1. Evaluate the frequency of sarcopenia among hospitalized patients and study the impact of different diagnostic criteria on sarcopenia diagnosis (Chapter I.a).
    1.2. Identify factors associated with sarcopenia and increase the knowledge about clinical (Chapter I.b) and financial impact (Chapter I.c) of sarcopenia among hospitalized patients.

2. Explore potential sources of error in the assessment of body circumferences and skinfold thickness (Chapter II):
    2.1. Quantify the effect of posture on body circumferences among adults and older adults, associated with body mass index (Chapter IIa).
    2.2. Describe and explore differences between several individual characteristics in the compressibility of triceps skinfold and factors associated with compressibility (Chapter IIb).

Chapter I

Sousa AS, Guerra RS, Fonseca I, Pichel F, Amaral TF

Sarcopenia among hospitalized patients – A cross-sectional study

Clin Nutr. *2014 [published online]*

Sousa AS, Guerra RS, Fonseca I, Pichel F, Amaral TF

Sarcopenia and length of hospital stay

Under review

Sousa AS, Guerra RS, Fonseca I, Pichel F, Ferreira S, Amaral TF

Financial impact of sarcopenia on hospitalization costs

Under review

Chapter I.a

Sarcopenia among hospitalized patients

– A cross-sectional study

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Original article

Sarcopenia among hospitalized patients — A cross-sectional study

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S U M M A R Y

Background & aims: Data on the prevalence of sarcopenia among hospitalized older patients are scarce and there is no available information on the burden of sarcopenia among younger patients. The present study aims to increase the knowledge about the frequency of sarcopenia among hospitalized patients and to evaluate the influence of different diagnostic criteria in these estimates.

Methods: A cross-sectional study was conducted in hospitalized adult patients. Sarcopenia was defined, according to the European Working Group on Sarcopenia in Older People (EWGSOP), as the presence of both low muscle mass, assessed by Bioelectrical Impedance Analysis (BIA), adjusted for height, and low muscle function (hand grip strength). Two other criteria were applied, also using hand grip strength for evaluating muscle function, one that also assessed muscle mass by BIA, but adjusted for weight, and another which estimated muscle mass based on mid-arm muscle circumference. Nutritional status was evaluated by Patient-Generated Subjective Global Assessment. The degree of agreement between the different diagnostic criteria was assessed using kappa. Multivariable logistic regression models were used in order to identify factors associated with sarcopenia.

Results: 608 hospitalized adult patients aged ≥18 years composed the study sample. According to EWGSOP's criteria, 25.3% patients were sarcopenic. However, depending on age and on the applied criteria, frequency of sarcopenia varied from 5% to 41.1% for men and from 4.9% to 38.3% for women. There was 95.7% ($k = 0.89$) agreement between criteria that estimated muscle mass by BIA. According to EWGSOP criteria approximately 20% of the non-undernourished patients were sarcopenic. Furthermore, 29.5% of overweight and 18.7% of obese patients were sarcopenic. Factors associated with sarcopenia were male gender, age ≥65 years, moderate or severe dependence, being undernourished and admitted to a medical ward.

Conclusions: Sarcopenia is frequent among hospitalized patients and varies widely depending on the applied diagnostic criteria. Sarcopenia was identified in a considerable proportion of patients aged under ≥65 years and in non-undernourished, namely among overweight and obese.

1. Introduction

Sarcopenia is a condition characterized by progressive loss of skeletal muscle mass and strength with ageing [1] and is associated with physical disability, low quality of life and higher mortality [1,2]. Sarcopenia strongly impacts health status and is also a contributor to frailty, which is a debilitating geriatric syndrome [1].

This is a highly frequent condition, estimated to occur between 5 and 45% of community dwelling older adults [3–5] as this figure depends on the reference population and diagnostic criteria used. Data on the agreement of different sarcopenia diagnostic criteria is scarce but studies conducted in community settings [6,7] revealed that sarcopenia prevalence is greatly dependent on the applied diagnostic criteria.

The term "sarcopenia" was defined for the first time in 1989 by Rosenberg [8]. Since then, numerous proposals have been put forward in order to establish a clinically applicable definition with diagnostic criteria and respective cut-off points [7]. In 2010, the European Consensus on Definition and Diagnosis of Sarcopenia

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described sarcopenia as a combination of both low muscle mass and low muscle function [1]. As the cut-offs for the diagnosis of sarcopenia depend both on the assessment technique used and on the reference studies available [1], the Consensus suggests Dual X-Ray Absorptiometry (DXA) or Bioelectrical Impedance Analysis (BIA) techniques and provides several cut-off points for each technique.

The use of BIA or DXA is not always viable for clinical practice and anthropometric measures are often used as a method for quantifying muscle mass [9]. As far as we are concerned, it has not been studied if using muscle mass estimated by anthropometrical measures or based on BIA evaluations generates different prevalences of sarcopenia.

Although sarcopenia is mainly identified in older adults, it can also be present in younger adults, especially when associated with illnesses as dementia and osteoporosis [1,10]. A recent study from 2013 by Cherin et al. [10] showed that sarcopenia was frequent among healthy community dwelling subjects over 45 years. Nevertheless, according to our knowledge, data on the problem of sarcopenia among hospitalized younger adults is lacking and this condition needs to be documented.

As sarcopenia has been associated with poor prognoses [11] and poor clinical outcomes in hospitalized patients [9], an early diagnosis is important in order to guide therapeutic procedures and to reduce the adverse consequences this condition entails. However, information about the prevalence of sarcopenia among hospitalized older patients is scarce and there are no available data on the prevalence of sarcopenia among younger patients. Therefore, the present study aims to increase the knowledge about the frequency of sarcopenia among hospitalized patients using different diagnostic criteria.

2. Materials and methods

2.1. Study population and design

A cross-sectional study was conducted in a general and teaching hospital between July 2011 and June 2013. A consecutive sampling method was applied in medical and surgical wards.

Patients were eligible to participate in the study if they were aged 18 and over, Caucasian, with an expected hospital stay longer than 24 h, conscious, cooperative and capable of providing written informed consent.

Patients unable to perform the hand grip strength (HGS) technique were excluded from the study. This lack of ability in carrying out HGS was defined as an inability to understand verbal instructions or having a condition limiting HGS measurement (namely pain). Critically ill patients, i.e., with a life-threatening medical or surgical condition requiring intensive care unit level care, presenting severe organ system dysfunction and needing for active therapeutic support were excluded [12]. Pregnancy and isolation were also defined as exclusion criteria. According to these criteria, patients admitted to neurology, haematology and intensive care unit wards were not recruited and participants from the following departments were selected: angiology and vascular surgery, cardiology, digestive surgery, endocrinology, gastroenterology, hepatobiliary surgery, internal medicine, nephrology, non-digestive surgery, orthopaedics, otorhinolaryngology and urology. Therefore, from the daily list of inpatients admitted to each ward, those who fulfilled inclusion criteria were invited to participate in the study, until the number of patients had attained the total number of beds of the ward.

From 897 patients who fulfil the inclusion criteria and were invited to participate, 289 (32.2%) were not included. The reasons were refusals ($n = 186$), cognitive impairment ($n = 13$) and unfinished study protocol ($n = 1$). Moreover, patients who did not have BIA results ($n = 84$) or mid-arm muscle circumference measurement ($n = 5$) were excluded from the study.

2.2. Ethics

This research was carried out according to the recommendations established by the Declaration of Helsinki and approved by the Institutional ethics and review boards of Centro Hospitalar do Porto. All study participants provided a written informed consent.

2.3. Data collection

Demographical and clinical data at the time of evaluation were retrieved from patient's clinical file. All other information was obtained through a structured questionnaire within 72 h of admission to hospital.

Education was evaluated by the number of completed school years and the following categories were created: 0–4, 5–12 and more than 12 years. Marital status was categorized as single, married or in a civil partnership, divorced and widowed. Cognitive impairment was evaluated with the Abbreviated Mental Test (AMT) [13]. Independence in activities of daily living was assessed with Katz index [14].

Patient nutritional status was evaluated with Patient-Generated Subjective Global Assessment (PG-SGA) [15]. Standing height (cm) was measured with a metal tape (Rosscraft, Innovations Incorporated, Surrey, Canada) with a 0.1 cm resolution and a headboard. Mid-arm circumference was obtained with the same metal tape. Body weight (kg) was assessed with a calibrated portable beam scale with a 0.5 kg resolution. Triceps skinfold thickness (mm) was obtained with a Harpenden® calliper (Baty International, Burgess Hill, UK) with a 0.2 mm resolution. All anthropometric measurements were performed by two previously trained nutritionists using standard methods [16]. The intra- and inter-observer technical error of measurement was calculated for all measurements, respectively, in 17 and 18 individuals. Intra-observer ranged from 0.2% to 0.6%, and inter-observer error ranged from 0 to 1.4%. These values are considered acceptable for trained anthropometrists [17].

BMI was determined through the standard formula [weight (kg)/height^2 (m)]. BMI categories were created according to the World Health Organization cut-offs [18] and according to Nutrition Screening Initiative (NSI) cut-offs, specific for older adults [19].

Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People (EWGSOP) as the presence of both low muscle mass and low muscle function [1]. Three different diagnostic criteria [2,3,20] and respective cut-off points were used, as shown in Table 1. Janssen et al. 2004 [20] criteria are presented as diagnostic criteria by the EWGSOP Consensus and are therefore used as a reference in estimating sarcopenia frequency.

Muscle mass was evaluated through mid-arm muscle circumference (MAMC) and by bioelectrical impedance analysis (BIA) (Biodynamics Model 450, Seattle, Washington USA). Mid-arm muscle circumference (cm) was calculated from mid-arm circumference (MAC) and triceps skinfold thickness (TSF) with the formula delivered by Jelliffe [21]: MAC − (3.14 × TSF). Muscle mass (kg) was obtained using the bioelectrical impedance analysis equation of Janssen et al. (2000) [22]: [(height^2/bioelectrical impedance analysis resistance × 0.401) + (gender × 3.825) + (age × −0.071)] + 5.102, with height measured in cm; bioelectrical impedance analysis resistance measured in ohms; for gender, men = 1 and women = 0; and age measured in years.

Muscle function was evaluated as HGS, using a calibrated Jamar® Hydraulic Hand dynamometer (Sammons Preston, Bolingbrook, IL,

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Table 1
Diagnostic criteria and respective cut-off points used to identify sarcopenia.

	Criteria	Formula	Cut-off points	HGS (kgf)
Muscle mass by BIA	Janssen et al. (2002) [3]	Skeletal muscle mass/body mass × 100%	<37% (men) <28% (women)	<30 (men) <20 (women)
	Janssen et al. (2004) [20]	Skeletal muscle mass/height^2	<10.75 kg/m^2 (men) <6.75 kg/m^2 (women)	
Muscle mass by MAMC	Landi et al. [2]	MAC − (3.14 × TSF)	<21.1 cm (men) <19.2 cm (women)	

BIA: bioelectric impedance analysis; HGS: hand grip strength; MAC: mid-arm circumference; MAMC: mid-arm muscle circumference; TSF: triceps skinfold thickness.

USA), with a 0.1 kgf resolution, proposed by the American Society of Hand Therapists as the "gold standard" for measurements of HGS [23]. Each subject undertook three measurements with a one minute interval between them and the maximum value was selected [24]. Low HGS was classified using the cut-offs proposed in the EWGSOP Consensus [1]: less than 30 kgf for men and 20 kgf for women.

2.4. Statistics

Frequency of sarcopenia was evaluated considering gender and age stratification (<65 years; ≥ 65 years) and by nutritional status according to PG-SGA categories.

Normality of variables distribution was evaluated through the Kolmogorov–Smirnov test. According to the normality of variables distribution, results were described as mean and standard deviation or as median and interquartile range (IQR). Categorical variables were reported as frequencies.

Association between muscle mass measured by BIA or estimated by MAMC was assessed using Spearman's correlation coefficient. The degree of agreement between the three diagnostic criteria of sarcopenia was evaluated using kappa with the Fleiss classification [25].

A multivariable logistic regression model was conducted to identify factors associated with sarcopenia.

Statistical significance was set at $p < 0.05$. All analyses were conducted with the Software Package for Social Sciences (SPSS) for Windows (version 20.0; SPSS, Inc., Chicago, IL).

3. Results

Characteristics of the 608 patients enrolled in this study, according to age and gender are presented in Table 2. Approximately one half (45.7%) patients were women, age ranged between 18 and 90 years old (median (IQR) = 57(21) years) with 68.3% patients aged under 65 and 4.6% aged over 80 years. Excluded patients were

Table 2
Participants' characteristics stratified by gender and age groups.

Age group (years)	Men		Women	
	<65 (n = 218)	≥65 (n = 112)	<65 (n = 197)	≥65 (n = 81)
Age (years), median (IQR)	52.5 (17.0)	70.1 (7.0)	48.0 (20.0)	74.0 (17.0)
School years, n (%)[a]				
0–4	68 (31.5)	56 (50.0)	67 (34.0)	57 (70.4)
5–12	133 (61.6)	39 (34.8)	111 (56.3)	20 (24.7)
>12	15 (6.9)	16 (14.3)	19 (9.6)	4 (4.9)
Marital status, n (%)				
Single	45 (20.6)	3 (3.0)	50 (25.4)	7 (10.9)
Married	140 (64.2)	93 (83.0)	118 (59.9)	33 (5.6)
Divorced	29 (13.3)	6 (5.4)	18 (9.1)	1 (1.6)
Widower	4 (1.8)	10 (8.9)	11 (5.6)	23 (35.9)
AMT, median (IQR)	10.0 (1.0)	10.0 (1.0)	9.0 (1.0)	9.0 (1.0)
Katz índex, n (%)				
Independent	200 (91.7)	97 (86.6)	180 (81.4)	61 (75.3)
Moderate dependence	9 (4.1)	10 (8.9)	10 (5.1)	11 (13.6)
Severe dependence	9 (4.1)	5 (4.5)	7 (3.6)	9 (11.1)
PG-SGA, n (%)				
Non-undernourished	126 (58.0)	52 (46.4)	120 (60.9)	30 (37.0)
Moderate/severe undernutrition	91 (42.0)	59 (52.7)	77 (39.1)	51 (63.0)
BMI categories, n (%)				
Underweight	8 (3.7)	3 (2.7)	4 (2.0)	2 (2.5)
Normal weight	95 (43.6)	51 (45.5)	81 (41.4)	20 (24.7)
Overweight	78 (35.8)	45 (40.2)	55 (27.9)	32 (39.5)
Obesity	37 (17.0)	13 (11.6)	57 (28.9)	27 (33.3)
BMI categories (NSI)[b], n (%)				
Underweight	–	22 (19.6)	–	11 (13.3)
Normal weight	–	60 (53.6)	–	27 (33.3)
Obesity	–	30 (26.8)	–	43 (53.1)
HGS (KgF), median (IQR)	34.3 (12.0)	28.4 (10.0)	18.2 (9.6)	13.0 (7.1)
MAMC (cm), mean (SD)	25.4 (3.0)	24.4 (2.6)	22.1 (3.3)	22.8 (3.1)

AMT: abbreviated mental test; PG-SGA: patient-generated subjective global assessment; BMI: body mass index; HGS: hand grip strength; MAMC: mid-arm muscle circumference; NSI: nutrition screening initiative.
[a] 3 missing values.
[b] Age-specific BMI cut-off points.

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Table 3
Frequency of sarcopenia using three different criteria, stratified by gender, age groups and nutritional status according to Patient-Generated Subjective Global Assessment (PG-SGA).

	Men			Women		
	Age group (years)			Age group (years)		
	<65 (n = 218)	≥65 (n = 112)	Total (n = 330)	<65 (n = 197)	≥65 (n = 81)	Total (n = 278)
Sarcopenia, n (%)						
Janssen et al. (2002)	46 (21.1)	38 (33.9)	84 (25.4)	31 (15.7)	31 (38.3)	62 (22.3)
Janssen et al. (2004)	52 (23.9)	46 (41.1)	98 (29.7)	30 (15.2)	26 (32.1)	56 (20.1)
Landi et al.	11 (5.0)	10 (8.9)	21 (6.4)	22 (11.2)	4 (4.9)	26 (9.4)

	Nutritional status (PG-SGA)				Nutritional status (PG-SGA)			
	Non-undernourished (n = 180)	Moderate undernutrition (n = 77)	Severe undernutrition (n = 73)	Total (n = 330)	Non- undernourished (n = 150)	Moderate undernutrition (n = 63)	Severe undernutrition (n = 65)	Total (n = 278)
Sarcopenia, n (%)								
Janssen et al. (2002)	32 (17.8)	27 (35.1)	25 (34.2)	84 (25.4)	29 (19.3)	14 (22.2)	19 (29.2)	62 (22.3)
Janssen et al. (2004)	37 (20.6)	33 (42.9)	28 (38.4)	98 (29.7)	25 (16.7)	11 (17.5)	20 (30.8)	56 (20.1)
Landi et al.	2 (1.1)	11 (14.3)	8 (11.0)	21 (6.4)	14 (9.3)	6 (9.5)	6 (9.2)	26 (9.4)

older than participants (median age 69.0 (IQR:16.0) vs 58.0 (IQR:21.5), $p < 0.001$).

Nutritional status evaluation according to PG-SGA showed that nearly half of the patients were undernourished (45.4% men and 46% women) and patients aged ≥65 years were more likely to be moderate or severely undernourished than younger patients (Table 2).

Frequency of sarcopenia according to the three used criteria and stratified by age groups and gender is presented in Table 3. Janssen et al. 2002 and Janssen et al. 2004 criteria identified a higher frequency of sarcopenic patients (respectively, 24% and 25.3%) than Landi et al. criteria (7.7%). Janssen et al. 2002 and 2004 criteria both identified a higher proportion of sarcopenic men than sarcopenic women but the opposite was found according to Landi et al. criteria.

Sarcopenia according to the three criteria stratified by gender and nutritional status classified by PG-SGA is presented in Table 3. According to the two diagnostic criteria of Janssen et al., similar proportions of patients were found to be simultaneously undernourished and sarcopenic, 14% for Janssen et al. 2002 criteria and 15.1% for Janssen et al. 2004 criteria. A lower frequency of patients were simultaneously undernourished and sarcopenic (5.1%) according to Landi et al. criteria. Otherwise, among non-undernourished patients, approximately 20% were sarcopenic by Janssen et al. 2002 criteria and Janssen et al. 2004 criteria.

According to Janssen et al. 2004 criteria, 41.2% of the underweight patients (classified by BMI categories) were sarcopenic.

Table 4
Frequency of sarcopenia in different hospital wards.

	Non-sarcopenic (n = 454)	Sarcopenic (n = 154)
Surgical wards[a]		
Angiology and Vascular	25 (5.5)	10 (6.5)
Digestive	40 (8.8)	6 (3.2)
Non-digestive	40 (8.8)	5 (3.9)
Hepatobiliary surgery	38 (8.4)	9 (5.8)
Orthopaedics	48 (10.6)	19 (12.3)
Otorhinolaringology	26 (5.7)	3 (19.5)
Urology	55 (12.1)	11 (7.1)
Medical wards[a]		
Cardiology	14 (3.1)	8 (5.2)
Endocrinology	18 (4.0)	7 (4.5)
Gastroenterology	18 (4.0)	5 (3.2)
Internal medicine	90 (19.8)	52 (33.8)
Nephrology	42 (9.3)	19 (12.3)

[a] Comparison between sarcopenia in surgical wards vs medical wards: $p < 0.001$.

However, sarcopenia was also present in a considerable percentage of overweight (29.5%) and obese patients (18.7%).

A moderate correlation was found ($r = 0.59$) between muscle mass measured by BIA and estimated by MAMC. An agreement of 95.7% ($k = 0.89$) between Janssen et al. 2002 and Janssen et al. 2004 criteria was found. Agreement for Landi et al. criteria versus Janssen et al. 2002 and Janssen et al. 2004 criteria was lower, 71.2% ($k < 0$) and 72.2% ($k = 0.05$), respectively.

Frequency of sarcopenia was assessed for each hospital ward and displayed in Table 4. A higher proportion of sarcopenic patients was found in medical wards than in surgical wards ($p < 0.001$).

As shown in Table 5, factors associated with sarcopenia were male gender, age ≥65 years, having moderate or severe dependence, being undernourished and being admitted to a medical ward.

4. Discussion

Sarcopenia is highly frequent among hospitalized adults. According to Janssen et al. 2004 criteria, a quarter of the hospitalized patients were sarcopenic (25.3%) and this condition is most often observed in older age groups. Our results also show that approximately one in five patients aged less than 65 years was sarcopenic. Frequency of sarcopenia was higher in men than in women and these results are in line with the previously described by Cherin et al. (2013) [10] amongst healthy subjects.

Sarcopenia occurrence estimates varied according to the different diagnostic criteria applied. For all age groups, this condition was less frequent when the Landi et al. criteria was used. As far as we are aware, there are no previous results comparing different sarcopenia diagnostic criteria among hospitalized patients, but our results are in line with the data from two other studies conducted in a middle aged and older community dwelling adults cohort [7,26].

Present results showed a very good agreement between Janssen et al. 2002 and 2004 criteria. This was to be expected because both are based on BIA for muscle mass estimate. In the first one muscle mass is adjusted for weight and in the other muscle mass is adjusted for height. This agreement was much higher than the agreement found between these two and Landi et al. criteria, perhaps this is due to the fact that these criteria are based on anthropometric measures (MAMC) for muscle mass estimate. Anthropometric measures are more susceptible to errors of estimation caused by changes in fat deposits and loss of skin elasticity

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Table 5
Factors associated with sarcopenia using a multivariable logistic regression model.

	Non-sarcopenic (n = 454)	Sarcopenic (n = 154)	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Gender, n (%)						
Male	232 (51.1)	98 (63.6)	1.68 (1.15–2.44)	0.007	1.92 (1.27–2.92)	0.002
Female	222 (48.9)	56 (36.4)	1 (referent)		1 (referent)	
Age, n (%)						
<65	333 (73.3)	82 (53.2)	1 (referent)		1 (referent)	
≥65	121 (26.7)	72 (46.8)	2.42 (1.66–3.63)	<0.001	2.00 (1.32–3.05)	0.001
School years, n (%)[a]						
0–4	170 (37.6)	78 (51.0)	1.73 (1.19–2.50)	0.004	1.43 (0.95–2.17)	0.090
≥5	282 (62.4)	75 (49.0)	1 (referent)		1 (referent)	
Marital status, n (%)						
Single	83 (18.3)	25 (16.2)	1 (referent)		1 (referent)	
Non- single	371 (81.7)	129 (83.8)	1.15 (0.71–1.88)	0.566	0.82 (0.47–1.42)	0.472
Katz index, n (%)						
Independent	440 (96.9)	138 (89.6)	1 (referent)		1 (referent)	
Dependent	14 (3.1)	16 (10.4)	3.64 (1.74–7.66)	<0.001	2.80 (1.25–6.27)	0.012
PG-SGA, n (%)						
Non-undernourished	268 (59.0)	62 (40.3)	1 (referent)		1 (referent)	
Moderate/severe undernutrition	186 (41.0)	92 (59.7)	2.13 (1.47–3.09)	<0.001	1.65 (1.10–2.49)	0.017
BMI categories, n (%)						
Underweight	10 (2.2)	7 (4.5)	2.18 (0.80–5.98)	0.782	1.13 (0.74–1.72)	0.576
Normal weight	187 (41.2)	60 (39.0)	1 (referent)		1 (referent)	
Overweight and obesity	257 (56.6)	87 (56.5)	1.06 (0.72–1.54)	0.782	1.95 (0.65–5.82)	0.232
Smoking habbits, n (%)						
Non-smoker	360 (79.3)	132 (85.7)	1 (referent)		1 (referent)	
Smoker	94 (20.7)	22 (14.3)	0.64 (0.39–1.06)	0.082	0.68 (0.39–1.20)	0.185
Cancer diagnosis, n (%)						
Absent	382 (84.1)	126 (81.8)	1 (referent)		1 (referent)	
Present	72 (15.9)	28 (18.2)	1.18 (0.73–1.71)	0.502	1.25 (0.74–2.10)	0.403
Hospital ward, n (%)						
Surgical	272 (59.9)	63 (40.9)	1 (referent)		1 (referent)	
Medical	182 (40.1)	91 (59.1)	2.16 (1.49–3.13)	<0.001	2.06 (1.38–3.06)	<0.001

BMI: body mass index; CI: confidence interval; OR: odds ratio; PG-SGA: patient-generated subjective global assessment.
[a] 3 missing values.

due to the ageing process [1]. Therefore, although anthropometric measures are widely recognized as being an easier and more feasible method than BIA for use in clinical practice, the EWGSOP does not recommend anthropometric measures for the diagnosis of sarcopenia [1].

Sarcopenia has been described among community dwelling older adults or those residing in care homes but there is little data about prevalence of sarcopenia among hospitalized older patients. Gariballa and Alessa (2013) [9] using Landi et al. criteria to define sarcopenia among acutely ill older patients reported a prevalence of 10%. Using the same criteria, a value of 7.3% was found in the present study for patients within the same age group. Smoliner et al. (2014) [27] on a study conducted on hospitalized geriatric patients where muscle mass was estimated by BIA and sarcopenia was identified using EWGSOP criteria, reported a 25.3% prevalence. Using the same criteria, our results revealed a higher prevalence (37.3%) of sarcopenia among patients aged over 65 years.

The present study results show that sarcopenia is also highly frequent in hospitalized adult patients aged under 65 years. Although we are not aware of previous investigations on the burden of sarcopenia in this aforementioned age group, Cherin et al. [10] using DXA to estimate muscle mass, showed that 9% of the individuals aged between 45 and 54 years and 13.5% of those aged 55–64 years were sarcopenic. We found higher frequencies but these differences are to be expected and can be explained by the different techniques used to estimate muscle mass and the diverse health conditions of the subjects enrolled in these studies.

Along with the previously described results, this study also identified a relevant proportion of patients simultaneously undernourished and sarcopenic, confirming that these conditions coexist. On the other hand, our results importantly reveal that sarcopenia occurs in non-undernourished patients and emphasise the importance of assessing sarcopenia in hospitalized patients. According to our knowledge, there is only one study from 2013 [28] which evaluated the prevalence of sarcopenia among critically ill patients classified as non-undernourished.

Considering that undernutrition and sarcopenia are known to be associated with a worse prognosis and negative clinical outcomes as well as with an increase in hospital length of stay, these findings suggest that it could be important to include the assessment of sarcopenia as a routine procedure in nutritional status evaluation, besides the presence of undernutrition.

As expected, according to Janssen et al. 2004 criteria, a considerable proportion of sarcopenia was identified among overweight and obese patients. These data show that sarcopenia is not associated only with underweight but also with overweight and obesity. Moreover, obesity may impair the accurate identification of sarcopenic patients by health care professionals.

The present study shows that sarcopenia, according to Janssen et al. 2004 criteria, is not only present but is also highly frequent among hospitalized younger patients. However, it is noteworthy that cut-off points and all three criteria used were previously created for use in older adults, as sarcopenia was considered as a geriatric condition. This situation may have biased present results with a possible underestimation of the frequency of sarcopenia. Moreover, it is also important to notice that young patients diagnosed as sarcopenic may also be cachectic and cachexia may contribute to sarcopenia development. Notwithstanding this, present findings reinforce the existing gap concerning age specific cut-offs for diagnosis of sarcopenia in younger adults.

Besides, patients from intensive care units and other critical patients were excluded from the present study due to their inability to perform functional tests, which are required to identify sarcopenia. This situation may limit the comparison between studies

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because critical patients due to their clinical condition, would be likely to present muscle mass depletion and reduced function and, therefore, to be sarcopenic. Furthermore, the inclusion of muscle function (physical performance) in the definition and diagnostic criteria of sarcopenia may impair the identification of sarcopenia among critical patients and patients unable to perform functional tests. Moreover, it is important to highlight that HGS of patients unable to stand was measured with individuals on a bed. Although a differential may exist between measurements performed with the individual in a sitting or lying position, care was taken in order to follow strictly HGS measurement protocol [24]. Specifically, HGS was obtained from all participants with the unsupported elbow [29].

In the present study, muscle mass was estimated through BIA, instead of using CT or MRI, the golden standards for quantifying muscle mass, or DXA the selected alternative for estimating muscle mass in research and clinical use [1]. This could be regarded as a study limitation. However, BIA results are readily reproducible and this is an economical, practical and portable method which, used under standard conditions, has been found to be a good alternative to DXA [1]. Although BIA may not be reliable in conditions like heart failure, kidney failure, and dehydration, after applying inclusion criteria, not all patients with these conditions were excluded. This may have led to a misclassification of muscle mass and subsequently some sarcopenic patients may not have been identified.

According to hospital discharge records, the proportion of discharged patients aged over 65 years old was 38.3% in 2012 and 40% in 2013. Our sample is composed of a lower proportion of patients aged over 65 years, of 31.7%. This may have led to a lower representation of a relevant group of high risk patients, underestimating sarcopenia burden. Nevertheless, the diagnostic criteria of sarcopenia recommended by the European Consensus requires the application of functional tests, thus excludes patients that are unable to perform them [30]. The lower representation of older patients in this sample may be explained by the need to comply with the criteria.

Several strengths of this study could be highlighted. A large number of hospitalized patients composed this study sample, with a wide age range, 18–90 years old. The patients enrolled in the present study were from a multiplicity of hospital surgical and medical wards, which ensured a large variety of diagnoses and different diseases. These characteristics strengthen the generalizability of our results for other hospitalized patients.

In order to appraise the clinical impact of sarcopenia, it would be important to reach a more specific, or even universal, consensus regarding cut-off points and diagnostic criteria of sarcopenia, providing more accurate information.

In conclusion, according to the diagnostic criteria from the EWGSOP, sarcopenia is frequent among hospitalized patients and this condition was identified in adult patients aged under 65 years. Furthermore, a considerable proportion of non-undernourished patients were sarcopenic and among overweight and obese patients, there was also a significant proportion of sarcopenia.

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Chapter I.b

Sarcopenia and length of hospital stay

Sarcopenia and length of hospital stay

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Abstract

Background/Objectives: We aimed to quantify the association of sarcopenia with length of hospital stay (LOS) and to identify factors associated with sarcopenia among hospitalized patients.

Subjects/Methods: 655 patients composed the study sample. A longitudinal study was conducted in a university hospital. Sarcopenia was defined, according to European Consensus criteria, as low muscle mass (bioelectrical impedance analysis) and low muscle function (handgrip strength). Logistic regression, Kaplan-Meier and Cox adjusted proportional hazards methods were used. LOS was determined from the date of hospital admission and discharge home (event of interest).

Results: Participants were aged 18 to 90 years (24.3% sarcopenic). Factors associated with sarcopenia were male gender, age ≥65 years, moderate or severe dependence, undernutrition and being admitted to a medical ward. Sarcopenic patients presented a lower probability of being discharged home (Hazard Ratio (HR), 95% Confidence Interval (CI) = 0.71, 0.58-0.86). However, after stratifying for age groups, this effect was visible only in patients aged <65 years (HR, 95% CI= 0.66, 0.51-0.86). Moreover, sarcopenic overweight or obese patients presented a higher probability of being discharged home (HR, 95% CI = 0.78, 0.61-0.99) than non-overweight sarcopenic patients (HR, 95% CI = 0.63, 0.48-0-83).

Conclusions: Being male, aged ≥65 years, presenting dependence, being undernourished and admitted to a medical ward were factors associated with sarcopenia among hospitalized adult patients. Sarcopenia is independently associated with longer LOS, although this association is stronger for patients aged

<65 years. Moreover, sarcopenic overweight was associated with a higher probability of discharge home than non-overweight sarcopenia.

Key-words: sarcopenia; handgrip strength; hospital; survival analysis; length of stay

Introduction

According to the European Working Group on Sarcopenia in Older People (EWGSOP) sarcopenia is defined as a combination of both low muscle mass and low muscle function [1]. This condition has been associated with physical disability, low quality of life and higher mortality [1, 2].

Sarcopenia is estimated to occur between 5 to 45% of community dwelling older adults [3-5]. While this condition is mainly observed in older adults, it can also be present in younger individuals. A study from 2013 by Cherin *et al.* [6] showed that 9% of the individuals aged between 45 and 54 years and 13.5% of those aged from 55 to 64 years were sarcopenic. Although data concerning sarcopenia in hospitalized patients are scarce, previous studies have described this condition as frequent among hospitalized older patients [7-11], ranging from 10% to 37.3%. Moreover, it has been recently shown that sarcopenia is present in hospitalized patients aged under 65 years, with a frequency equal to 19.8% [10].

It has been previously reported that sarcopenia is related with poor clinical outcome in hospitalized older patients, namely higher mortality [7, 9, 12], higher risk of non-elective readmission in a six month period [7] and worst post-operative outcomes [13-16].

In a study conducted among hospitalized patients aged ≥65 years [7], sarcopenic patients presenting a mean age of 79 years were reported to have higher length of hospital stay (LOS) than non-sarcopenic patients. In contrast, Cerri *et al.* (2014) [9] found no differences in LOS between sarcopenic and non-sarcopenic patients, among hospitalized older patients, with a mean age of 84.2 years, ranging from 66 to 100 years. Nevertheless, as far as we are concerned, there are no available data on the impact of sarcopenia on LOS among hospitalized patients aged <65 years. LOS is an indicator of the changes that occur during a hospitalization process and can be used as a surrogate marker of health status (17). Moreover, predicting LOS may lead to a maximization of resources (18).

According to our knowledge, data on factors associated with sarcopenia in hospitalized patients are scarce while it is particularly limited among hospitalized younger patients. Moreover, the potential effect of confounding factors on the association between sarcopenia and LOS remains to be described. Identification of sarcopenia and the establishment of an association between this condition and LOS are of utmost importance in order to provide a more effective healthcare plan and thus reducing the adverse consequences this condition entails.

This study aims to quantify the association of sarcopenia with LOS, after adjustment for potential confounders and to identify factors associated with sarcopenia among a wide-ranging sample of hospitalized adult patients.

Materials and Methods

Study sample and design

A longitudinal study was conducted in a general, university and 600 beds hospital between July 2011 and December 2014. A consecutive sampling method was applied in medical and surgical wards. Patients were eligible to participate in the study if they were aged 18 years and over, Caucasian, with an expected hospital stay longer than 24 hours, conscious, cooperative and capable of providing written informed consent.

Patients unable to perform the handgrip strength (HGS) technique were excluded from the study. This impossibility in carrying out HGS measurement was defined as an inability to understand verbal instructions or having a condition limiting HGS measurement (namely pain). Critically ill patients, *i.e.*, with a life-threatening medical or surgical condition requiring intensive care unit level care, presenting severe organ system dysfunction and needing for active therapeutic support were excluded [(19)]. Pregnancy and patient ward isolation were also defined as exclusion criteria. According to these criteria, patients admitted to neurology, clinical haematology and intensive care unit wards were not recruited whereas participants from the following departments were selected: angiology and vascular surgery, cardiology, digestive surgery, endocrinology, gastroenterology, hepatobiliary surgery, internal medicine, nephrology, non-digestive surgery, orthopaedics, otorhinolaryngology and urology. Therefore, from the daily list of inpatients admitted to each of these wards, those who fulfilled inclusion criteria were invited to participate in the study, until the number of patients had attained the total number of beds of the ward.

From 992 patients who fulfilled the inclusion criteria and were invited to participate, 337 (34%) were not included. The reasons were refusals (n=198), cognitive impairment (n=13) and missing data (n=126).

All patients were followed up from the time of admission until death, hospital discharge or 30 days after admission.

Ethics

This research was carried out according to the recommendations established by the Declaration of Helsinki and approved by the Institutional ethics and review boards of *Centro Hospitalar do Porto*. All study participants provided a written informed consent.

Data collection

Demographical, clinical data, medical diagnoses and data of hospital admission were retrieved from patient's clinical file at the time of evaluation. Date of hospital discharge, discharge destination (home, another ward, another hospital, continuing care unit and discharge against medical advice or death) and discharge diagnosis were retrieved from hospital records after patient discharge. All other information was obtained by two trained registered nutritionists through a structured questionnaire within 72h of admission to hospital.

Education was evaluated by the number of completed school years and the following categories were created: 0-4, 5-12 and more than 12 years. Marital status was categorized as single, married or in a civil partnership, divorced and widowed. Cognitive impairment was evaluated with the Abbreviated Mental Test (AMT) [20].

Independence in activities of daily living was assessed with the Katz index [(21)]. Charlson disease severity index [(22)] was obtained by two previously trained interviewers using medical discharge diagnoses in the patient's clinical record.

Patient nutritional status was evaluated with Patient - Generated Subjective Global Assessment (PG-SGA) [(23)]. Standing height (cm) was measured with a metal tape (Rosscraft, Innovations Incorporated, Surrey, Canada) with a 0.1 cm resolution and a headboard. Body weight (kg) was assessed with a calibrated portable beam scale with a 0.5 kg resolution. All anthropometric measurements were performed by two previously trained registered nutritionists using standard methods [(24)]. The intra- and inter- observer technical error of measurement was calculated for all measurements, respectively, in 17 and 18 individuals. Intra-observer ranged from 0.2% to 0.6%, and inter-observer error ranged from 0 to 1.4%. These values are considered acceptable for trained anthropometrists [(25)].

Body mass index (BMI) was determined through the standard formula [weight (kg) / height^2 (m)] and BMI categories were created according to the World Health Organization cut-offs [(26)].

Sarcopenia was defined according to the EWGSOP as the presence of both low muscle mass and low muscle function [(1)].

Whole body resistance (ohms) and reactance (ohms) were assessed through tetrapolar bioelectrical impedance analysis (BIA) using a Biodynamics Model 450 (Seattle, Washington USA) with 0.1 ohm resolution, operating at a single frequency of 50 KHz.

Muscle mass was evaluated using the equation of Janssen *et al*. (2000) [(27)]: $[(\text{height}^2/\ \text{resistance} \times 0.401) + (\text{gender} \times 3.825) + (\text{age} \times -0.071)] + 5.102$, with height measured in cm; resistance measured in ohms; for gender, men = 1 and women = 0; age measured in years. Muscle mass was adjusted for height. Gender specific cut-off points indicated in the EWGSOP consensus were used [1].

Muscle function was evaluated as HGS, using a calibrated Jamar® Hydraulic Hand dynamometer (Sammons Preston, Bolingbrook, IL, USA), with a 0.1 kgf resolution. The Jamar® dynamometer is proposed by the American Society of Hand Therapists as the gold standard for measurements of HGS [28]. Each subject undertook three measurements using the non-dominant hand with a one minute interval between measurements and the maximum value was selected [29]. Low HGS was classified using the cut-offs proposed in the EWGSOP Consensus [1]: less than 30 kgf for men and 20 kgf for women.

Statistics

According to the normality of variables distribution, evaluated through Kolmogorov-Smirnov test, results were described as mean and standard deviation or as median and interquartile range (IQR) if non-normal distribution. Categorical variables were reported as frequencies.

In order to identify variables associated with sarcopenia by bivariable analysis, sarcopenic and non-sarcopenic patients were compared for several demographic and clinical characteristics. Bivariable and multivariable logistic regression models were also conducted. Variables were included in the multivariable logistic regression model considering their potential confounding effect. Length of hospital stay was dichotomized according to a cut-off of 7 days based on the median LOS of the entire sample, and in agreement with the median

LOS in Portuguese hospitals [30]. Variables associated with longer LOS (≥7 days) were identified comparing patients with and without a long LOS. All the comparisons were computed using Mann-Whitney test, or Student's t test for independent samples, for continuous variables and Pearson χ^2 or Fisher's exact test for categorical variables.

Length of hospital stay was determined from the date of hospital admission and discharge to usual residence (the main event of interest). Patients who were not discharged from the hospital to usual residence within the study period were censored at the time of other events, namely death, transfer (to another hospital ward, to another hospital or to continuing care units) and discharge against medical advice (n=40). Length of hospital stay was censored at 30 days, so patients that remained hospitalized 30 days after hospital admission were also censored (n=16). The Kaplan-Meier method was used to estimate the cumulative probability of being discharge-free over time (*i.e.* to experience the event of interest, defined as discharge home within the follow-up interval), according to the presence or the absence of sarcopenia.

Multivariable Cox proportional hazards regression models were used to estimate adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI). The following characteristics were considered in the multivariable procedure: presence of sarcopenia (categorical), age (categorical), Charlson index (continuous), nutritional status categories according to PG-SGA (categorical), education (categorical), Katz index (categorical), gender (categorical), marital status (categorical) and AMT (continuous).

Statistical significance was set at $p < 0.05$. All analyses were conducted with the Software Package for Social Sciences (SPSS) for Windows (version 20.0; SPSS, Inc., Chicago, IL).

Results

Baseline characteristics of the 655 hospitalized patients enrolled in this study, according to sarcopenia status are shown in Table 1. Approximately half of patients were women (46.1%), age ranged between 18 and 90 years old (median (IQR) = 56 (22) years). Frequency of sarcopenia was 24.3%. Within the period the present study was conducted two patients had died. Therefore, mortality rate was 0.3%.

Sarcopenic patients were older and presented longer LOS than non-sarcopenic patients (Table 1). Also, they were more likely to be male, to be undernourished and to present higher Charlson index score than non-sarcopenic patients (Table 1). There was a higher proportion of sarcopenic patients in medical wards than in surgical wards. The highest proportion of sarcopenic patients (34.3%) was observed in internal medicine wards. Otorhinolaryngology presented the lowest proportion of sarcopenic patients (1.9%).

It is worth noticing that patients aged ≥ 65 years presented lower muscle mass (median (IQR) 24.8 (11.4) kg) than patients aged < 65 years (median (IQR) 26.4 (11.4) kg), p= 0.008. Older patients also presented lower HGS than patients aged<65 years (median (IQR) 22.0 (9.8) kgf versus median (IQR) 24.1 (17.5) kgf), p<0.001.

As shown in Table 2, after adjusting for potential confounders, being a male, aged ≥65 years, presenting moderate or severe dependence, being undernourished and being admitted to a medical ward were factors associated with sarcopenia.

Table 1 – Participants' baseline characteristics according to sarcopenia status.

	Non-sarcopenic (n=496)	**Sarcopenic (n=159)**	***p***
Age (years), median (IQR)	54 (24.0)	64 (19.0)	<0.001 [2]
Age categories, n (%)			
< 65	367 (74.0)	85 (53.5)	
≥ 65	129 (26.0)	74 (46.5)	<0.001 [1]
Gender, n (%)			
Women	244 (49.2)	58 (36.5)	
Men	252 (50.8)	101 (63.5)	0.006 [1]
Education (years), n (%)			
0-4	183 (36.9)	81 (50.9)	
5-12	270 (54.4)	64 (40.3)	0.005 [1]
>12	43 (8.7)	14 (8.8)	
Marital status, n (%)			
Single	91 (18.3)	25 (15.7)	
Non-single	405 (81.7)	134 (84.3)	0.477 [1]
AMT, median (IQR)	10.0 (1.0)	10.0 (1.0)	0.437 [2]
Charlson Index, median (IQR)	1.0 (2.0)	2.0 (3.0)	0.002 [2]
PG-SGA, n (%)			
Non-undernourished	298 (60.1)	63 (39.6)	<0.001 [1]
Undernourished	198 (39.9)	96 (60.4)	

Table continued

Table 1 continued

	Non-sarcopenic (n=496)	**Sarcopenic (n=159)**	***p***
Katz index, n (%)			
Independent	481 (97.0)	143 (89.9)	0.001 [1]
Moderate / severe dependence	15 (3.0)	16 (10.1)	
BMI categories, n (%)			
Underweight	11 (2.2)	8 (5.0)	
Normal weight	207 (41.7)	62 (39.0)	0.173[1]
Overweight /obesity	278 (56.0)	89 (56.0)	
Hospital ward, n (%)			
Medical	223 (45.0)	96 (60.4)	
Surgical	273 (55.0)	63 (39.6)	0.001 [1]
LOS, days, median (IQR)	6.0 (6.0)	9.0 (10.0)	<0.001 [2]
LOS, days, n (%)			
<7	251 (50.6)	55 (34.6)	
≥7	245 (49.4)	104 (65.4)	<0.001 [1]
HGS (kgf), median (IQR)			
Women	18.0 (9.4)	13.0 (6.5)	<0.001 [2]
Men	35.4 (8.0)	23.4 (7.2)	<0.001 [2]
Muscle Mass (kg), median (IQR)	26.2 (11.8)	24.9 (6.7)	0.002 [2]

IQR, Interquartile range; AMT, Abbreviated Mental Test; PG-SGA, Patient-Generated Subjective Global Assessment; BMI, body mass index; LOS, length of hospital stay; HGS, handgrip strength.

[1] Chi-square test or Fisher's Exact test; [2] Mann-Whitney test;

Table 2 - Factors associated with sarcopenia using a bivariable and a multivariable logistic regression model.

	Crude OR (95%CI)	***p***	**Adjusted OR (95%CI)**	***p***
Age categories, n (%)				
< 65	1		1	
≥ 65	2.48 (1.71-2.44)	<0.001	2.01 (1.34-3.02)	0.001
Gender, n (%)				
Women	1		1	
Men	1.69 (1.17-2.44)	0.005	1.83 (1.22-2.72)	0.003
Education (years), n (%)				
0-4	1.36 (0.70-2.62)	0.360	1.23 (0.60-2.55)	0.573
5-12	0.73 (0.38-1.41)	0.347	0.75 (0.36-1.56)	0.447
>12	1		1	
Marital status, n (%)				
Single	1		1	
Non-single	1.20 (0.74-1.95)	0.451	1.23 (0.72-2.12)	0.453
PG-SGA, n (%)				
Non-undernourished	1		1	
Undernourished	2.29 (1.59-3.30)	<0.001	1.74 (1.16-2.60)	0.008
Katz index, n (%)				
Independent	1		1	
Dependent	3.59 (1.73-7.44)	0.001	2.50 (1.14-5.46)	0.022
BMI categories, n (%)				
Underweight	1.07 (0.74-1.55)	0.725	1.18 (0.78-1.79)	0.429
Normal weight	1		1	
Overweight /obesity	2.43 (0.94-6.30)	0.068	2.00 (0.72-5.61)	0.184
Hospital ward, n (%)				
Medical	1.86 (1.30-2.68)	0.001	1.74 (1.18-2.56)	0.005
Surgical	1		1	
LOS, days, n (%)				
<7	1		1	
≥7	1.94 (1.34-2.81)	<0.001	1.47 (0.98-2.22)	0.064

OR, Odds Ratio; CI, confidence interval;

PG-SGA, Patient-Generated Subjective Global Assessment; BMI, body mass index; LOS, length of hospital stay

Participants' characteristics were also stratified according to LOS (< 7 days and ≥ 7 days), as presented in Table 3. Compared to patients with a short LOS, patients with longer hospital stay were older, had a lower education level, were less likely to be single, presented a lower AMT score, were more likely to be dependent according to Katz index, were less likely to be overweight or obese, presented reduced HGS, were more likely to be undernourished, sarcopenic and presented a higher Charlson index score.

Table 3 – Participants' characteristics stratified according to length of hospital stay (LOS) (days).

	LOS < 7 (n=306)	LOS ≥ 7 (n=349)	*p*
Gender, n (%)			
Women	146 (47.7)	156 (44.7)	0.480 [1]
Men	160 (52.3)	193 (55.3)	
Age, median (IQR)	53 (25.3)	59 (21.0)	<0.001 [2]
Education (years), n (%)			
0-4	120 (39.2)	144 (41.3)	
5-12	150 (49.0)	184 (52.7)	0.033 [1]
>12	36 (11.8)	21 (6.0)	
Marital status, n (%)			
Single	66 (21.6)	50 (14.3)	0.018 [1]
Non-single	240 (78.4)	299 (85.7)	
AMT, median (IQR)	10.0 (1.0)	9.0 (1.0)	0.004 [2]
Katz index, n (%)			
Independent	300 (98.0)	324 (92.8)	0.002 [1]
Moderate/Severe dependence	6 (2.0)	25 (7.2)	
PG-SGA, n (%)			
Non-undernourished	214 (69.9)	147 (42.1)	<0.001 [1]
Undernourished	92 (30.1)	202 (57.9)	
Sarcopenia, n (%)			
Non-sarcopenic	251 (82.0)	245 (70.2)	0.002 [1]
Sarcopenic	55 (18.0)	104 (29.8)	
BMI categories, n (%)			
Underweight	6 (2.0)	13 (3.7)	
Normal Weight	117 (38.2)	152 (43.6)	0.018 [1]
Overweight / obesity	183 (59.8)	184 (52.7)	
HGS (kgf), median (IQR)	25.3 (14.8)	22.9 (18.0)	<0.001 [2]
Charlson Index, median (IQR)	1.0 (2.0)	2.0 (3.0)	0.005 [2]

IQR, interquartile range; AMT, Abbreviated Mental Test; PG-SGA, Patient-Generated Subjective Global Assessment; BMI, body mass index; HGS, handgrip strength.

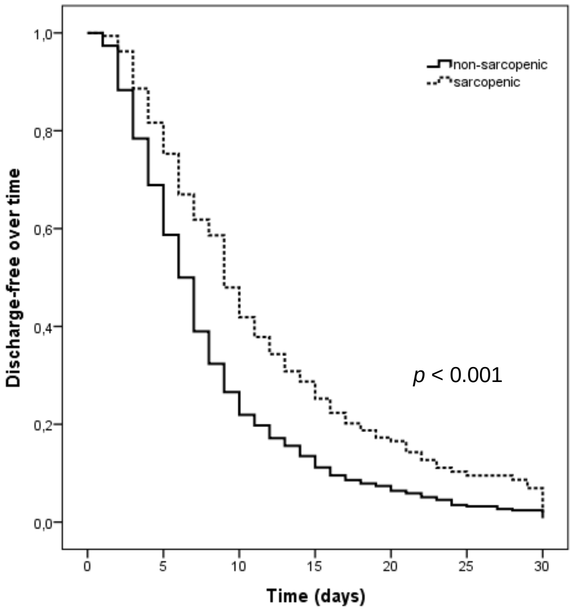
[1] Chi-square test or Fisher's Exact test; [2] Mann-Whitney test;

Figure 1 shows the probability of being discharge-free over time according to the presence of sarcopenia, considering all the participants (Figure 1A), and stratified by age groups, < 65 years (Figure 1B) and ≥ 65 years (Figure 1C). Sarcopenic patients presented a lower probability of experiencing the event of interest (being discharged home), as displayed in Figures 1A and 1B. However, for patients aged ≥ 65 years, this effect was no longer visible (Figure 1C).

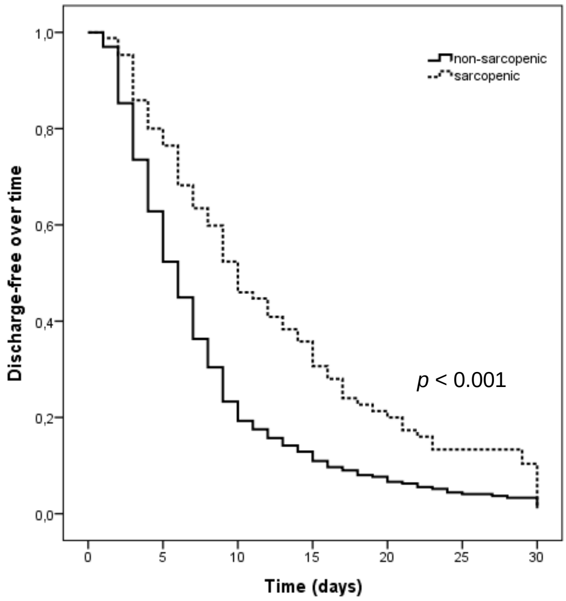
The association of sarcopenia with overweight or obesity (BMI ≥ 25 kg/m^2) was also evaluated. From all sarcopenic patients (n=159), 44% presented only sarcopenia and 56% of the patients were simultaneously overweight (or obese) and sarcopenic. It is noteworthy that sarcopenic patients who were simultaneously overweight or obese presented higher muscle mass than non-overweight sarcopenic patients, median 25.5 (12.4) kg vs median 24.1 (9.8) kg, p<0.001, and also higher muscle mass adjusted for height, mean 10.1 (2.0) kg/m^2 vs mean 9.1 (1.7) kg/m^2, p<0.001. Compared with non-sarcopenic patients, sarcopenic patients present a lower probability of being discharged home. However, patients with non-overweight sarcopenia presented a lower probability of being discharged home compared with sarcopenic overweight patients (p<0.001) (Figure 1D).

Figure 1 - Probability of being discharge-free over time according to sarcopenia status.

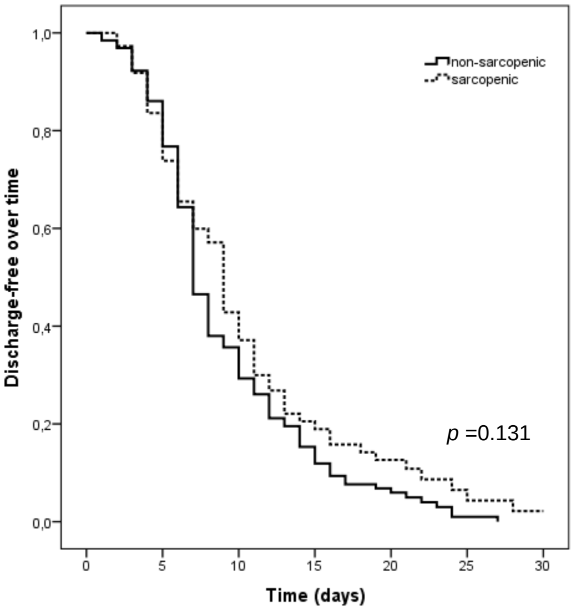
A: entire sample



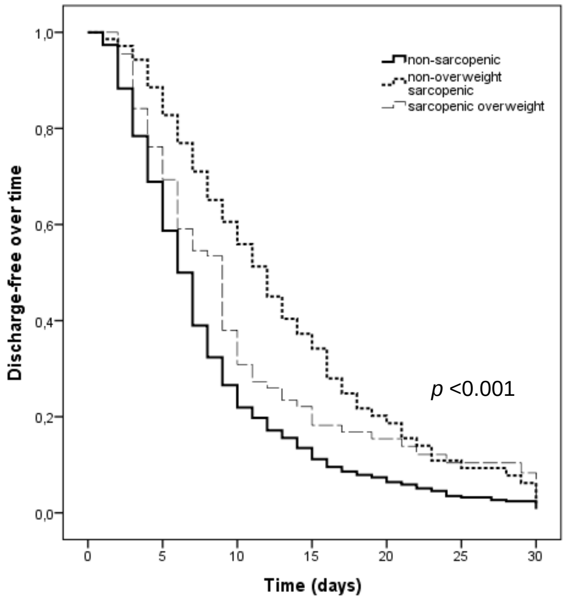
B: age < 65 years



C: age ≥ 65 years



D: entire sample (overweight and non-overweight patients)



Results from multivariable Cox proportional hazards regression models were displayed for the entire sample and according to age groups (Table 4). The model was adjusted for age, gender, marital status, education, nutritional status, Charlson index, AMT score and Katz index, as these variables could be considered as potential confounders in the association between sarcopenia and LOS.

Considering the entire sample and the group of patients aged < 65 years, sarcopenia was consistently associated with lower HR (<1) for being discharged home, meaning that sarcopenic patients presented a lower probability of being discharged home. However, for patients aged ≥ 65 years, sarcopenia was not independently associated with the probability of being discharged home.

It is worth noticing that sarcopenic overweight or obese patients presented a higher probability of being discharged home, adjusted HR (95% CI) = 0.78 (0.61-0.99) than non-overweight sarcopenic patients, adjusted HR (95% CI) = 0.63 (0.48-0.83).

Additionally, LOS had also been stratified according to hospital ward (medical or surgical) and, as expected, there was a higher proportion of patients with a longer LOS (≥7 days) admitted to medical wards (53%) than in surgical wards (47%), p=0.019. Thus, the type of hospital ward was included in an additional multivariable Cox proportional hazards regression model. However, the inclusion of this variable did not modify the results concerning the probability of being discharged home.

Table 4 - Hazard ratios (HR) of being discharged home associated with the presence of sarcopenia.

	All patients (n=655)		**Age < 65 years (n= 452)**		**Age ≥ 65 years (n= 203)**	
	Adjusted HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
Sarcopenia						
Non-sarcopenic	1		1		1	
Sarcopenic	0.71 (0.58-0.86)	0.001	0.66 (0.51-0.86)	0.002	0.80 (0.58-1.10)	0.168
Gender						
Female	1		1		1	
Male	1.00 (0.85-1.19)	0.969	0.97 (0.79-1.18)	0.754	1.18 (0.84-1.66)	0.328
Age (years)						
< 65	1		-	-	-	-
≥ 65	0.94 (0.78-1.13)	0.535	-	-	-	-
Education (years)						
0-4	1		1		1	
4-12	0.81 (0.67-0.97)	0.023	0.74 (0.59-0.93)	0.010	0.82 (0.59-1.14)	0.235
>12	1.24 (0.92-1.68)	0.156	1.23 (0.83-1.33)	0.293	0.92 (0.56-1.53)	0.759

Table continued

Table 4 continued

	All patients (n=655)		Age < 65 years (n= 452)		Age ≥ 65 years (n= 203)	
	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
Marital Status						
Single	1		1		1	
Non-single	0.87 (0.70-1.07)	0.190	0.82 (0.64-1.03)	0.094	1.22 (0.66-2.25)	0.531
AMT	1.05 (0.96-1.14)	0.301	1.10 (0.99-1.24)	0.079	0.98 (0.85-1.12)	0.733
Katz index						
Independent	1		1		1	
Moderate / Severe dependence	0.77 (0.52-1.14)	0.188	0.74 (0.45-1.23)	0.250	0.71 (0.38-1.31)	0.268
PG-SGA						
Non-undernourished	1		1		1	
Moderate / Severe undernutrition	0.56 (0.47-0.66)	<0.001	0.51 (0.41-0.62)	<0.001	0.70 (0.51-0.97)	0.030
Charlson index	0.94 (0.90-0.98)	0.003	0.95 (0.90-1.00)	0.068	0.90 (0.83-0.98)	0.010

CI, confidence interval; AMT, Abbreviated Mental Test; PG-SGA, Patient-Generated Subjective Global Assessment.

Discussion

The present study results show that sarcopenic patients presented a lower probability of being discharged from the hospital. Cox analysis revealed that sarcopenia is associated with longer LOS after considering the confounding effect of age, gender, marital status, education, nutritional status, disease severity, cognitive impairment and independence in daily living activities. However, after stratifying this analysis by age groups, this association was only observed for patients aged <65 years. This may be explained by a lower proportion of older patients in the study sample (approximately 31%), which leads to a loss of statistical power, increasing the possibility of occurrence of a type two error or, alternatively, by different clinical characteristics, *i.e.*, the simultaneous presence of several co-morbidities in older patients could have diminished the strength of the association of sarcopenia with LOS.

This study results increased the knowledge and highlighted the impact of sarcopenia on LOS, specifically among hospitalized younger patients (<65 years). Besides, as far as we are concerned, there were no previous data concerning factors associated with sarcopenia among hospitalized younger patients, with the exception for previous results from a recent study undertaken by our research team [(10)].

Gariballa and Alessa (2013) [(7)], in a study conducted among hospitalized older patients which defined sarcopenia with muscle mass assessed through mid-arm muscle circumference and muscle function evaluated by HGS, concluded that LOS was significantly higher in sarcopenic patients compared with non-sarcopenic patients. Otherwise, in a study conducted by Cerri *et al.* (2014) [(9)] among hospitalized undernourished older patients, no differences in LOS were found between sarcopenic and non-sarcopenic patients. Using similar methodology, our results for older patients corroborate Cerri *et al.* [(9)] findings. Although present results are not in accordance with Gariballa and Alessa, the observed differences between studies may be explained by the use of different methodology, BIA and anthropometry, in the assessment of muscle mass and by different patients' characteristics. However, our results clearly show a significant association of sarcopenia with prolonged LOS for patients aged under 65 years.

The difference observed for < 65 years and ≥ 65 years groups concerning the association of sarcopenia with LOS may be justified by the existence of different characteristics, diagnoses and, even, higher severity of co-morbidities between younger and older adult patients, besides the possible occurrence of a type two error, as hypothesized before in this section.

The present study results also showed that sarcopenic overweight or obese patients (BMI ≥ 25 kg/m^2) had a higher probability of being discharged home than sarcopenic non-overweight patients. A possible explanation is that overweight (or obese) patients presented significantly higher muscle mass than non-overweight patients. Thus, characteristics related to overweight and higher muscle mass could have introduced a protective effect for being discharged from the hospital. Notwithstanding this, due to the presence of overweight or obesity these patients may not present obvious frailty physical features. This may have influenced caregivers and biased the indication for discharge destination.

The present study shows a frequency of sarcopenia among hospitalized older adults of 36.4%, being higher than previous reports, 10% from Gariballa and Alessa (2013) [7], 25.3% from Smoliner *et al*.(2014) [8], 26% from Rossi *et al.* (2014) [11] and 21.4% from Cerri *et al.*(2014) [9]. These differences may be due to the use of different methodology and to patients' characteristics. This study also identified sarcopenia in 18.8% of the hospitalized patients aged under 65 years. However, it is noteworthy that cut-off points used were previously defined for use in older adults, as sarcopenia was considered as a geriatric condition. This situation may have biased present results with a possible under diagnosis of sarcopenia.

Patients from intensive care units and other critical patients were excluded from the present study due to their inability to perform the required functional tests to identify sarcopenia. This situation may constitute a study limitation because critical patients due to their clinical condition, would be likely to present muscle mass depletion and reduced function and, therefore, to be sarcopenic. Furthermore, the inclusion of muscle function (physical performance) in the definition and diagnostic criteria of sarcopenia may impair the identification of sarcopenia among critical patients and patients unable to perform functional tests. Moreover, it is important to highlight that HGS of patients unable to stand was measured with individuals on a bed. Although a differential may exist between measurements performed with the individual in a sitting or lying position, care was taken in order to follow strictly HGS measurement protocol [29]. Specifically, HGS was obtained from all participants with the unsupported elbow [31].

In the present study, muscle mass was estimated through BIA, instead of using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), the golden standards for quantifying muscle mass, or Dual Energy X-ray Absorptiometry (DXA) the selected alternative for estimating muscle mass in research and clinical use [1]. This could be regarded as a study limitation. However, BIA results are readily reproducible and this is an economical, practical and portable method which, used under standard conditions, has been found to be a good alternative to DXA (6). Although BIA may not be reliable in conditions like heart failure, kidney failure, and dehydration, after applying inclusion criteria, not all patients with these conditions were excluded. This may have led to a misclassification of muscle mass and subsequently to a misclassification of sarcopenia.

According to hospital discharge records, the proportion of discharged patients aged over 65 years was 38.3% in 2012 and 40% in 2013. Our sample contains less patients aged over 65 years (31%). This may have resulted in a lower representation of an important group of high risk patients, underestimating sarcopenia burden. Nonetheless, the diagnostic criteria of sarcopenia recommended by the European Consensus necessitate the application of functional tests, thus excluding patients who are unable to carry out these tests [9]. The lower representation of older patients in this sample may be explained by the need to fulfill the criteria.

Several strengths of this study could be highlighted. A large number of hospitalized patients composed this study sample, with a wide age range, 18 to 90 years old. The patients enrolled in the present study were from a multiplicity of hospital surgical and medical wards, which ensured a large variety of diagnoses and different diseases. These characteristics strengthen the generalizability of our results for other hospitalized patients.

Survival analysis has the ability of handling data that are censored, which in this study were death, transfer, discharge against medical advice and LOS>30 days. This allows for a better hospital representation, because it permits the inclusion of cases that could not be included with other statistical approaches, namely, with follow-up information unavailable after a certain point, which in our study was 30 days after hospital admission. Nonetheless, only 16 participants (2.4% of the study sample) had a LOS longer than 30 days, thus an extended follow-up period probably would not have changed the results obtained.

Although there are some results available concerning mortality and hospital readmission for older patients [7, 9, 12], further research is required in order to assess short-term and long-term consequences of sarcopenia in hospitalized patients.

Being male, aged ≥65 years, presenting dependence, being undernourished and being admitted to a medical ward are factors associated with sarcopenia among hospitalized adult patients. Sarcopenia is independently associated with longer LOS, although this association is stronger for patients aged < 65 years. Moreover, sarcopenic overweight is associated with a higher probability of discharge to usual residence than non-overweight sarcopenia.

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Conflicts of interest

The authors declare no conflicts of interest.

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Chapter I.c

Financial impact of sarcopenia on hospitalization costs

Financial impact of sarcopenia on hospitalization costs

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Abstract

Background and aims: Data on the association of sarcopenia with costs among hospitalized patients are limited to surgical patients. This study aims to increase knowledge regarding the association of sarcopenia with these costs among a wide-ranging sample of surgical and non-surgical patients.

Methods: A prospective study was conducted among hospitalized adult patients. Sarcopenia was identified according to the European Working Group on Sarcopenia in Older People, as low muscle mass, assessed by bioelectrical impedance analysis and low muscle function evaluated by handgrip strength. Hospitalization cost was calculated for each patient based on discharge diagnosis related group codes and determined on the basis of a relative weight value. Costs were defined as the percentage of deviation from the cost of a patient with a relative weight equal to one. Multivariable linear regression models were performed to identify the factors independently associated to hospitalization costs.

Results: 656 hospitalized patients aged ≥18 years (24.2% sarcopenic) composed the study sample. Sarcopenia increased hospitalization costs by €1240 (95 % CI: €596-1887) for patients aged <65 years and €721 (95% CI: €13-1429) for patients aged ≥65 years. Sarcopenic overweight was related to an increase in hospitalization costs of €884 (95% CI: €295-1476).

Conclusion: Sarcopenia is independently related to hospitalization costs. This condition is estimated to increase hospitalization costs by 58.5% for patients aged <65 years and 34% for patients aged ≥65 years.

Key-words: sarcopenia; body composition; handgrip strength; hospital; cost

Introduction

Sarcopenia is currently defined as a combination of both low muscle mass and low muscle function, according to the European Working Group on Sarcopenia in Older People (EWGSOP) (1).

It is estimated that sarcopenia occurs between 5 to 45% of community dwelling older adults (2-4). Although this condition has been mainly described in older adults, it can also be present in younger individuals. Cherin *et al*. in a study conducted among community dwelling adults (5) showed that 9% of the individuals aged between 45 and 54 years and 13.5% of those aged from 55 to 64 years were sarcopenic. Previous studies have shown that this condition is highly frequent among hospitalized older patients (6-10), ranging from 10% to 37.3% and was identified in circa one fifth of patients aged under 65 years (9).

This condition has been associated with physical disability, low quality of life and higher mortality in community dwelling older adults (1, 11). Among hospitalized patients, sarcopenia has been related with poor clinical outcome, namely worst post-operative outcomes (12-15), higher risk of non-elective readmission (6) and higher mortality (6, 8, 16).

Considering the impact of sarcopenia on both community dwelling and hospitalized individuals, healthcare costs of this condition are expected to be high (17). However, according to our knowledge, data on the economic burden of sarcopenia are limited. One study from 2004 (18), conducted among representative samples of American adults aged ≥ 60 years, reported that the estimated healthcare cost attributable to sarcopenia defined as the loss of muscle mass was $18.5 billion

($10.8 billion in men, $7.7 billion in women). Recent studies from 2013 (19) and 2015 (20, 21), reported that sarcopenia determined by computed tomography scans, was associated with increased costs in major surgery. Nevertheless, the impact of sarcopenia on hospitalization costs among a wider variety of patients, from surgical and non-surgical wards, remains to be documented.

Considering the adverse consequences sarcopenia entails among hospitalized patients and the financial constraints that healthcare systems often face, it is important to recognize and explore the association of sarcopenia with hospitalization costs, in order to maximize resources and provide a more effective healthcare plan.

Therefore, the present study aims to increase the knowledge on the association of sarcopenia with costs among a wide-ranging sample of hospitalized patients.

Materials and Methods

Study sample and design

A prospective study was conducted in a general and university hospital between July 2011 and December 2014. A consecutive sampling method was applied in medical and surgical wards. Patients were eligible to participate in the study if they were aged 18 years and over, Caucasian, with an expected hospital stay longer than 24 hours, conscious, cooperative and capable of providing written informed consent.

Patients unable to perform the handgrip strength (HGS) technique were excluded from the study. This impossibility in carrying out HGS measurement was defined as an inability to understand verbal instructions or having a condition limiting HGS measurement (namely pain). Critically ill patients, *i.e.*, with a life-threatening medical or surgical condition requiring intensive care unit level care, presenting severe organ system dysfunction and needing for active therapeutic support were excluded (22). Pregnancy and patient ward isolation were also defined as exclusion criteria.

According to these criteria, patients admitted to neurology, clinical haematology and intensive care unit wards were not recruited whereas participants from the following departments were selected: angiology and vascular surgery, cardiology, digestive surgery, endocrinology, gastroenterology, hepatobiliary surgery, internal medicine, nephrology, non-digestive surgery, orthopaedics, otorhinolaryngology and urology. Therefore, from the daily list of inpatients admitted to each of these wards, those who fulfilled inclusion criteria were invited to participate in the study, until the number of patients had attained the total number of beds of the ward.

From 992 patients who fulfilled the inclusion criteria and were invited to participate, 336 (33.9%) were not included. The reasons were refusals (n=198), cognitive impairment (n=13) and missing data (n=125).

Ethics

This research was conducted according to the recommendations established by the Declaration of Helsinki and approved by the Institutional ethics and review boards of *Centro Hospitalar do Porto*. All study participants provided written informed consent.

Data collection

Demographical, clinical data, medical diagnoses and data of hospital admission were retrieved from patient's clinical file at the time of evaluation. Date of hospital discharge and discharge diagnosis were retrieved from hospital records after the patient had left the hospital. All other information was obtained by two trained registered nutritionists through a structured questionnaire within 72h of admission to the hospital.

Education was evaluated by the number of completed school years and the following categories were created: 0-4, 5-12 and more than 12 years. Marital status was categorized as single and not single (married or in a civil partnership, divorced and widowed). Cognitive impairment was evaluated with the Abbreviated Mental Test (AMT) (23). Independence in activities of daily living was assessed with the

Katz index (24) and two categories were defined according to the score obtained: ≤ 5 - moderate / severe dependence and 6 - independent. Charlson Disease Severity Index (25) was recorded by two previously trained interviewers using medical discharge diagnoses in the patient's clinical record.

Patient nutritional status was evaluated with Patient - Generated Subjective Global Assessment (PG-SGA) (26). Standing height (cm) was measured with a metal tape (Rosscraft, Innovations Incorporated, Surrey, Canada) with a 0.1 cm resolution and a headboard. Body weight (kg) was assessed with a calibrated portable beam scale with a 0.5 kg resolution. All anthropometric measurements were performed by two previously trained registered nutritionists using standard methods (27). The intra-and inter-observer technical error of measurement was calculated for all measurements, respectively, in 17 and 18 individuals. Intra-observer ranged from 0.2% to 0.6%, and inter-observer error ranged from 0 to 1.4%. These values are considered acceptable for trained anthropometrists (28).

Sarcopenia was defined according to the EWGSOP as the presence of both low muscle mass and low muscle function (1).

Whole body resistance (ohms) and reactance (ohms) were assessed through tetrapolar bioelectrical impedance analysis (BIA) using a Biodynamics Model 450 (Seattle, Washington USA) with 0.1 ohm resolution, operating at a single frequency of 50 KHz.

Muscle mass was evaluated using the equation of Janssen *et al*. (2000) (29): $[(\text{height}^2/ \text{resistance} \times 0.401) + (\text{gender} \times 3.825) + (\text{age} \times -0.071)] + 5.102$, with height measured in cm; resistance measured in ohms; for gender, men = 1 and women = 0; age measured in years. Muscle mass was adjusted for height. Gender specific cut-off points indicated in the EWGSOP consensus were used (1).

Muscle function was evaluated by HGS, using a calibrated Jamar® Hydraulic Hand dynamometer (Sammons Preston, Bolingbrook, IL, USA), with 0.1 kgf resolution. The Jamar® dynamometer is proposed by the American Society of Hand Therapists as the gold standard for measurements of HGS (30). Each subject undertook three measurements using the non-dominant hand with a one minute interval between measurements and the maximum value was selected (31). Low HGS was classified using the cut-offs proposed in the EWGSOP Consensus (1): less than 30 kgf for men and 20 kgf for women.

Body mass index (BMI) was determined through the standard formula [weight (kg) / height^2 (m)] and BMI categories were created according to the World Health Organization cut-offs (32).

Statistics

According to the normality of variables distribution, evaluated through Kolmogorov-Smirnov test, results were described as mean and standard deviation or as median and interquartile range (IQR) if non-normal distribution. Categorical variables were reported as frequencies.

Hospitalization cost was calculated for each patient based on discharge diagnosis related group (DRG) codes. The DRG system is used to calculate hospital reimbursements, with the amounts determined on the basis of a relative weight value. This weight value reflects the main diagnosis, surgical interventions, pathologies, complications, clinical procedures, medium length of hospital stay, age, gender and discharge destination.

The information about DRG codes and its amounts was obtained from Portuguese Ministerial Directive number 839-A, 31 July 2009 (33) for data obtained between 2011 and 2012, number 163, 24 April 2013 (34) was used for data obtained in 2013 and number 20 from 29 January 2014 (35) was used for data obtained in 2014. The percentage of cost deviation was calculated from the difference between the cost of each patient and the cost of a patient with a relative weight equal to one (€2396 for data obtained between 2011 and 2012; €2142 for data obtained in 2013; €2120 for data obtained in 2014). Percentage of cost deviation was summarized into quartiles using the cutoffs of the sample distribution: ≤-35.3 (24.1%); -35.2,-1.10 (25.8%); -1.09, 88.4 (24.5%); ≥88.5 (25.6%).

Length of hospital stay (LOS) was determined from the date of hospital admission and discharge. Length of hospital stay was also dichotomized according to a cut-off of 7 days based on the median LOS of the entire sample, and in agreement with the median LOS in Portuguese hospitals (36).

In order to select variables associated with sarcopenia and with percentage of cost deviation, patients were compared for several demographic and clinical characteristics. All the comparisons were computed using Mann-Whitney test, or Student's *t* test for independent samples, or Kruskal-Wallis test for continuous variables and Pearson χ^2 for categorical variables.

Multivariable linear regression models using stepwise method were performed to identify the independent variables associated with percentage of cost deviation. The following variables were included in the model: sarcopenia status (categorical), age (continuous), gender (categorical), marital status (categorical), Katz index (categorical), education (categorical), nutrition status (categorical), hospital ward (categorical), length of hospital stay (categorical), the Abbreviated Mental Test score (continuous) and the Charlson comorbidity index score (continuous). These variables were included, as they were considered potential confounders.

Statistical significance was set at $p < 0.05$. All analyses were conducted with the Software Package for Social Sciences (SPSS) for Windows (version 20.0; SPSS, Inc., Chicago, IL).

Results

Baseline characteristics of the 656 hospitalized patients enrolled in this study, according to sarcopenia status are shown in Table 1. Approximately half of patients were women (46.1%), age ranged between 18 and 90 years old, median (IQR) = 56 (22) years. Sarcopenia was highly frequent affecting 24.2% of the participants.

Sarcopenic patients were older and presented longer LOS than non-sarcopenic patients (Table 1). Also, sarcopenic patients were more likely to be male, to be undernourished and to present higher Charlson index score than non-sarcopenic patients (Table 1). There was a higher proportion of sarcopenic patients in medical wards than in surgical wards (Table 1). The highest proportion of sarcopenic patients (34.3%) was observed in internal medicine wards.

Hospitalization costs within the present sample ranged from €387 to €30880, median (IQR) of €2369 (€3094). Patients' characteristics were stratified according to the percentage of cost deviation quartiles, as shown in Table 2. Sarcopenic patients presented a positive percentage of cost deviation, *i.e.*, these patients present a mean cost higher than the cost of a patient with relative weight equal to one. Otherwise, the percentage of cost deviation was negative for non-sarcopenic patients. Thus, non-sarcopenic patients present a mean cost lower than the cost of a patient with relative weight equal to one.

Compared to patients in the upper quartiles of percentage of cost deviation, patients in the lower quartiles had a higher education level, were more likely to be single, were less likely to be dependent and presented better nutrition status and shorter length of hospital stay (Table 2). The highest proportion of sarcopenic patients was found in the highest quartile of percentage of cost deviation distribution.

There was a higher proportion of patients admitted to surgical wards in the two upper quartiles of percentage of cost deviation (Table 2).

Table 1 – Participants' baseline characteristics according to sarcopenia status.

	Non-sarcopenic (n=497)	**Sarcopenic (n=159)**	***p***
Age (years), median (IQR)	54 (24.0)	64 (19.0)	<0.001 [a]
Age categories, n (%)			
< 65	368 (74.0)	85 (53.5)	
≥ 65	129 (26.0)	74 (46.5)	<0.001 [b]
Gender, n (%)			
Women	244 (49.1)	58 (36.5)	
Men	253 (50.9)	101 (63.5)	0.006 [b]
Education (years), n (%)			
0-4	184 (37.0)	81 (50.9)	
5-12	270 (54.3)	64 (40.3)	0.005 [b]
>12	43 (8.7)	14 (8.8)	
Marital status, n (%)			
Single	91 (18.3)	25 (15.7)	
Not single	406 (81.7)	134 (84.3)	0.550 [b]
AMT, median (IQR)	10.0 (1.0)	10.0 (1.0)	0.455 [a]
Charlson Index, median (IQR)	1.0 (2.0)	2.0 (3.0)	0.002 [a]
PG-SGA, n (%)			
Non-undernourished	299 (60.2)	63 (39.6)	<0.001 [b]
Undernourished	198 (39.8)	96 (60.4)	

Table continued

Table 1 continued

	Non-sarcopenic (n=497)	**Sarcopenic (n=159)**	***p***
Katz index, n (%)			
Independent	482 (97.0)	143 (89.9)	0.001^{b}
Moderate / severe dependence	15 (3.0)	16 (10.1)	
BMI categories, n (%)			
Underweight	11 (2.2)	8 (5.0)	
Normal weight	207 (41.6)	62 (39.0)	0.173^{b}
Overweight /obesity	279 (56.1)	89 (56.0)	
Hospital ward, n (%)			
Medical	223 (44.9)	96 (60.4)	
Surgical	274 (55.1)	63 (39.6)	0.001^{b}
LOS, days, median (IQR)	6.0 (6.0)	9.0 (10.0)	$<0.001^{a}$
LOS, days, n (%)			
<7	252 (50.7)	55 (34.6)	
≥7	245 (49.3)	104 (65.4)	$<0.001^{b}$
HGS (kgf), median (IQR)			
Women	18.0 (9.4)	13.0 (6.5)	$<0.001^{a}$
Men	35.5 (8.0)	23.4 (7.2)	$<0.001^{a}$
SMI (kg/m^2), mean (SD)			
Women	8.6 (1.4)	6.6 (1.0)	0.003^{c}
Men	11.1 (1.5)	9.4 (0.8)	$<0.001^{c}$
Percentage of cost deviation (€), median (IQR)	-5.1 (103.1)	44.3 (178.5)	$<0.001^{a}$

IQR, Interquartile range; SD: standard deviation; AMT, Abbreviated Mental Test; PG-SGA, Patient-Generated Subjective Global Assessment; SMI: skeletal muscle mass index (muscle mass / height^2); BMI, body mass index; LOS, length of hospital stay; HGS, handgrip strength.
[a] Mann-Whitney test; [b] Chi-square test; [c] Independent samples *t*-Test

Table 2 – Participants' characteristics according to percentage of cost deviation quartiles.

	Percentage of cost deviation quartiles				
	1st ≤-35.3 (n=158)	**2nd** -35.2,-1.10 (n=169)	**3rd** -1.09,88.4 (n=161)	**4th** ≥88.5 (n=168)	***p***
Gender, n (%)					
Women	77 (48.7)	78 (46.2)	69 (42.9)	78 (46.4)	
Men	81 (51.3)	91 (53.8)	92 (57.1)	90 (53.6)	0.770[a]
Age, median (IQR)	53.0 (30.3)	52.0 (23.0)	58.0 (21.0)	61.0 (18.5)	<0.001[b]
Education (years), n (%)					
0-4	46 (29.1)	68 (40.2)	65 (40.4)	86 (51.2)	
5-12	90 (57.0)	89 (52.7)	80 (49.7)	75 (44.6)	0.001[a]
>12	22 (13.9)	12 (7.1)	16 (9.9)	7 (4.2)	
Marital status, n (%)					
Single	35 (22.2)	34 (20.1)	31 (19.3)	16 (9.5)	
Not single	123 (77.8)	135 (79.9)	130 (80.7)	152 (90.5)	0.013[a]
AMT, median (IQR)	10.0 (1.0)	10.0 (1.0)	10.0 (1.0)	9.0 (2.0)	0.081[b]
Katz index, n (%)					
Independent	154 (97.5)	163 (96.4)	156 (96.9)	152 (90.5)	
Moderate/ severe dependence	4 (2.5)	6 (3.6)	5 (3.1)	16 (9.5)	0.008[a]
PG-SGA, n (%)					
Non-undernourished	103 (65.2)	100 (59.2)	85 (52.8)	74 (44.0)	
Undernourished	55 (34.8)	69 (40.8)	76 (47.2)	94 (56.0)	0.001[a]
Sarcopenia, n (%)					
Non-sarcopenic	128 (81.0)	138 (81.7)	128 (79.5)	103 (61.3)	
Sarcopenic	30 (19.0)	31 (18.3)	33 (20.5)	65 (38.7)	<0.001[a]
BMI categories, n (%)					
Underweight	2 (1.3)	5 (3.0)	8 (5.0)	4 (2.4)	
Normal weight	69 (43.7)	74 (43.8)	54 (33.5)	72 (42.9)	0.232[a]
Overweight / obesity	87 (55.1)	90 (53.3)	99 (61.5)	92 (54.8)	
Charlson Index, median (IQR)	2.0 (2.0)	1.0 (2.0)	2.0 (3.0)	2.0 (3.0)	0.264[b]
Hospital ward, n (%)					
Medical	94 (59.5)	91 (53.8)	81 (50.3)	53 (31.5)	
Surgical	64 (40.5)	78 (46.2)	80 (49.7)	115 (68.5)	<0.001[a]
LOS, days, median (IQR)	5 (5)	5(5)	8(7)	9 (9)	<0.001[b]
LOS, days, n (%)					
<7	103 (65.2)	97 (57.4)	64 (39.8)	43 (25.6)	
≥7	55 (34.8)	72 (42.6)	97 (60.2)	125 (74.4)	<0.001[a]

IQR, interquartile range; AMT, Abbreviated Mental Test; PG-SGA, Patient-Generated Subjective Global Assessment; LOS, length of hospital stay; BMI, body mass index;

[a] Chi-square test; [b] Kruskal-Wallis test;

Multivariable linear regression models calculated to predict the percentage of cost deviation are presented in Table 3. The analysis was displayed for the entire sample (model 1) and according to age groups, <65 years and ≥65 years (models 2 and 3). Additionally, model 4 considered sarcopenic overweight (sarcopenia associated with BMI ≥ 25 Kg/m^2) as an independent variable.

In model 1, being not single, undernourished, admitted to a surgical ward, having ≥7 days of hospitalization and being sarcopenic were associated to higher hospitalization costs. For patients who were aged < 65 years (model 2), age, admission to a surgical ward, undernutrition, ≥7 days of hospitalization and sarcopenia were associated to higher percentage of cost deviation. In model 3, for patients aged ≥65 years, admission to a surgical ward, ≥7 days of hospitalization and sarcopenia were also associated to higher hospitalization costs. Sarcopenic overweight or sarcopenic obesity (BMI ≥ 25 kg/m2) was also able to predict a higher percentage of cost deviation, together with age, undernutrition, admission to surgical ward and length of hospital stay (model 4).

After adjustment for potential confounders, the economic impact of sarcopenia in hospitalization cost in the entire sample it is estimated to be € 1117 (95% CI: € 644-1588), €1240 (95 % CI: €596-1887) for patients aged < 65 years and €721 (95% CI: €13-1429) for patients aged ≥65 years. Sarcopenic overweight is estimated to be associated with an increase of €884 (95% CI: €295-1476) in hospitalization costs.

Table 3 – Multivariable linear regression models for prediction of hospitalization cost.

	Regression coefficient (95% CI)	*p*
Model 1 (entire sample)		
Marital status (reference: single)	29.8 (5.27-54.2)	0.017
PG-SGA (reference: non-undernourished)	27.7 (8.08-47.4)	0.006
Hospital ward (surgical *vs* medical)	66.8 (47.9-85.6)	<0.001
LOS, days (reference: LOS < 7 days)	62.4 (42.8-81.9)	<0.001
Sarcopenia (reference: non-sarcopenic)	52.7 (30.4-74.9)	<0.001
Model 2 (age < 65 years)		
Age, years	1.31 (0.37-2.25)	0.007
PG-SGA (reference: non-undernourished)	28.5 (3.87-53.2)	0.023
Hospital ward (surgical *vs* medical)	51.8 (28.6-75.0)	<0.001
LOS, days (reference: LOS < 7 days)	59.0 (35.0-83.0)	<0.001
Sarcopenia (reference: non-sarcopenic)	58.5 (28.1-89.0)	<0.001
Model 3 (age ≥ 65 years)		
Hospital ward (surgical *vs* medical)	101.7 (69.5-134.0)	<0.001
LOS, days (reference: LOS < 7 days)	64.6 (31.2-98.0)	<0.001
Sarcopenia (reference: non-sarcopenic)	34.0 (0.60-67.4)	0.046
Model 4 (entire sample)		
Age, years	0.80 (0.19-1.41)	0.010
PG-SGA (reference: non-undernourished)	29.3 (9.4-49.1)	0.004
Hospital ward (surgical *vs* medical)	63.8 (45.0-82.7)	<0.001
LOS, days (reference: LOS < 7 days)	63.8 (44.0-83.5)	<0.001
Sarcopenic overweight, (reference: non-sarcopenic overweight)	41.7 (13.9-69.6)	0.003

CI, confidence interval; PG-SGA, Patient-Generated Subjective Global Assessment; LOS, length of hospital stay.

Variables included: sarcopenia or sarcopenic overweight status (non-sarcopenic used as reference), age, gender (women used as reference), marital status (single used as reference), Katz index (independent used as reference), education (dichotomized as 0-4 years and ≥ 5 years; ≥5 years was used as reference), undernutrition status according to PG-SGA (non-undernourished used as reference), hospital ward (surgical used as reference), length of hospital stay (<7 days used as reference), Abbreviated Mental Test score and Charlson comorbidity index score.

Dependent variable: percentage of cost deviation.

Discussion

The present study results show that sarcopenia is associated with a major increase in hospitalization costs, considering the effect of potential confounders. After stratifying the model according to age group, this effect was still visible for both younger and older adults, in spite of being stronger for younger patients.

It is worth highlighting that with the exception of sarcopenia, factors associated with hospitalization costs changed across the two different age groups. While age, undernutrition, being on a surgical hospital ward and length of stay were related to higher hospitalization costs for younger patients, in the model carried out for patients aged ≥ 65 years, only length of stay and the ward of hospitalization were associated with the percentage of cost deviation. Moreover, sarcopenic overweight (or obesity) was also a predictor of higher hospitalization costs, even though the association was weaker than the one described for sarcopenic patients.

Additionally, it is worth mentioning that the multivariable linear regression model was adjusted for length of hospital stay using a dichotomised variable (< 7 days, ≥7 days), although medium length of hospital stay is included in the weighing value used for calculate hospitalization cost. The inclusion of this variable in the multivariable analyses is justified by the existence of an interval of days of hospitalization for each DRG code. These defined intervals can be wide-ranging. Depending on the interval indicated to each DRG code, the same DRG code can be attributable to a patient with a short LOS (< 7 days) and a patient with a longer LOS (≥ 7 days). The potential confounding effect of different LOS was, therefore, controlled.

The present study results increase the knowledge about sarcopenia and hospitalization costs by providing an estimation on this association. Sarcopenia defined by computed tomography scans was related with higher costs among patients who underwent surgery (19, 20, 21). The ability of HGS, as a single parameter in predicting higher hospitalization costs has also been recently described (37). However, as far as we are concerned, there were no previous reports where sarcopenia was defined as low muscle mass and low muscle function and among hospitalized patients with a wide range of diagnoses and age. Therefore, due to differences in methodology, these results are not comparable with previous reports. The impact of sarcopenia in healthcare costs has been described in the United States (18). But, in this report, sarcopenia was defined merely by the loss of muscle mass and the observation was not focused on hospitalized patients.

The inclusion of muscle function (physical performance) in the definition and diagnostic criteria of sarcopenia may impair the identification of sarcopenia among critically ill patients and patients unable to perform functional tests. This situation may constitute a study limitation because these patients due to their clinical condition, would be likely to present muscle mass depletion and reduced function and, therefore, to be sarcopenic.

In the present study, muscle mass was assessed with BIA, instead of using computed tomography or magnetic resonance imaging which are the golden standards for quantifying muscle mass, or dual energy x-ray absorptiometry, the selected alternative for estimating muscle mass in research and clinical use (1). This could be a study limitation. However, BIA is an economical, practical and reproducible method which, used under standard conditions, has been described as a suitable alternative to dual energy x-ray absorptiometry (1). Although BIA may not be reliable in conditions like heart failure, kidney failure, and dehydration (29) not all patients with these conditions were excluded. This may have caused a misclassification of muscle mass and consequently a misclassification of sarcopenia.

According to hospital discharge records, the proportion of discharged older patients (aged ≥ 65 years) was 38.3% in 2012 and 40% in 2013.The proportion of patients aged over 65 years in our sample contains is lower (31%). This situation may have led to a lower representation of an important group of high risk patients, underestimating sarcopenia burden. Nevertheless, the diagnostic criteria of sarcopenia recommended by the European Consensus, requires the application of functional tests, thus excluding patients who are unable to carry out these tests (8). The lower representation of older patients in this sample may be explained by the need to comply with the criteria.

The DRG system has been shown to underestimate the real hospitalization costs as it reflects only direct hospitalization costs. Indirect costs, as societal costs, are not taken into account (38). Nonetheless, this methodology was used in the present study as it allows for an assortment of patients with a diversity of diagnoses and procedures.

Several strengths of this study could be emphasized. This sample is composed of a large number of hospitalized patients, with a wide age range, from 18 to 90 years old. The patients enrolled in the present study were from a multiplicity of hospital surgical and medical wards, which ensured a variety of diagnoses and diseases. These characteristics strengthen the generalizability of our results for other hospitalized patients.

Further investigation is needed in order to explore the extent of the influence of the early identification of sarcopenia in the reduction of adverse outcomes and, therefore, the reduction of inherent hospitalization costs.

In conclusion, present research shows that sarcopenia is independently related to hospitalization costs. This condition is estimated to increase hospitalization costs in 52.7% (58.5% for patients aged < 65 years and 34% for patients aged ≥ 65 years).

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The authors declare no conflicts of interest.

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Chapter II

Sousa AS; Fonseca I, Pichel F, Amaral TF

Effects of posture and body mass index on body girths assessment

Under review

Sousa AS; Fonseca I, Pichel F,, Amaral TF

Triceps skinfold compressibility in hospitalized patients – an exploratory analysis

Under review

Chapter II.a

Effects of posture and body mass index on body girths assessment

Effects of posture and body mass index on body girths assessment

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Key-words: anthropometry; posture; body mass index; body girths; body composition

Abstract

Background: The present study aims to evaluate the effect of posture on body girths assessment among hospitalized adults and older adults. We further explored the influence of body mass index on this effect.

Materials and Methods: A cross-sectional study was conducted among hospitalized adult patients. Arm, waist, hip and calf girths were obtained for each patient in standing and supine positions. Body girths were obtained in the two body positions and differences were compared according to body mass index (BMI) normal weight and overweight categories.

Results: 123 patients (27.6% aged ≥65 years) composed the study sample. Significant differences were found between measurements obtained in standing and supine positions, ranging from 0.6 to 1.1 cm. Intraclass Correlation Coefficient (ICC) values were ≥0.97 and agreement ranged from 81.3% to 87% (weighted k ≥0.84). Similar results were found when differences were stratified by BMI categories.

Conclusion: Although body girths assessment in standing and supine positions in hospitalized adults and older adults differ, these differences are small and they are not dependent on BMI categories.

Introduction

Current anthropometry protocols, specifically those for body girths assessment, indicate supine position as the correct position for performing measurements [1]. Nevertheless, in clinical practice, namely in hospital settings, there are often individuals who, due to a number of factors, are unable to change their body position for girth measurements [2,3]. In those cases, it is required to adapt the standard technique to the patient’s condition.

In the hospital environment, the effect of body posture on measurements is of utmost importance because anthropometry is a relevant resource for assessment and prognosis prediction. Moreover, body girths are frequently used for body composition and nutritional assessment purposes, isolated or as part of undernutrition diagnosis and screening tools [4-6].

A previous report had shown that, among young healthy adults, body posture influenced anthropometric measurements of the lower limbs [3]. More recently, a study conducted among institutionalized and hospitalized older adults (aged ≥65 years) showed that differences found between body girths obtained in both standing and supine positions did not have clinically relevant impact on nutritional status classification according to Mini Nutritional Assessment – Short Form and reference data percentiles [7].

Besides body posture, physical complexion can also be a source of error for anthropometric assessment and it is not currently known if differences associated with body posture are greater when anthropometric measurements are evaluated in overweight or obese subjects rather than in individuals with normal weight. Anthropometric measurements in obese (or overweight) patients, due to the presence of a larger body size are more susceptible to error, even with a trained anthropometrist. This possible influence of obesity (or overweight) in body girths assessment needs to be documented, as, in clinical practice, this effect can lead to a misinterpretation of anthropometry and, consequently, a misclassification of nutritional status.

According to our knowledge, there is no available information on the effect of posture on body girths among adult hospitalized patients aged <65 years. Moreover, there are no previous reports on the effect of different body mass index (BMI) categories and body complexion in body girths measurement. Therefore, the present study aims to evaluate the effect of posture on body girths assessment among hospitalized adults and older adults. We further explored the influence of body mass index on this effect.

Materials and Methods

Study sample and design

A cross-sectional study was conducted in a general university hospital. Patients were eligible to participate in the study if they were aged 18 years and over, Caucasian, conscious, cooperative, capable of changing body position from standing to supine and able to provide written informed consent.

Critically ill patients, *i.e.*, with a life-threatening medical or surgical condition requiring intensive care unit level care, presenting severe organ system dysfunction and needing for active therapeutic support were excluded [8]. Pregnancy and patient ward isolation were also defined as exclusion criteria. Patients with BMI <18.5 Kg/m^2 (n=5) were excluded from the analysis.

This research was carried out according to the recommendations established by the Declaration of Helsinki and approved by the institutional ethics and review boards. All study participants provided a written informed consent.

Data collection

Demographical data were obtained by a trained registered nutritionist through a structured questionnaire within 72h of admission to hospital.

Education was evaluated by the number of completed school years and the following categories were created: 0-4, 5-12 and more than 12 years. Marital status was categorized as single, married or in a civil partnership, divorced and widowed. Cognitive impairment was evaluated with the Abbreviated Mental Test (AMT) [9]. Independence in activities of daily living was assessed with the Katz index [10].

Patient nutritional status was evaluated with Nutritional Risk Screening 2002 [11]. Standing height (cm) was measured with a metal tape (Rosscraft, Innovations Incorporated, Surrey, Canada) with a 0.1 cm resolution and a headboard. Body weight (kg) was assessed with a calibrated portable beam scale with 0.5 kg resolution. Measurements of the arm, waist, hip and calf girths were performed by a previously trained registered nutritionist following standard methods [1] and using a metal tape with 1 mm resolution. All measurements were conducted first with the subject in a standing position and after with the subject in a supine position.

The intra- and inter- observer technical error of measurement was calculated for all measurements. Intra-observer ranged from 0.2% to 0.6%, and inter-observer error ranged from 0 to 1.4%. These values are considered acceptable for trained anthropometrists [12,13].

BMI was determined through the standard formula [weight (kg) / height^2 (m)] [14] and BMI categories were created according to the World Health Organization cut-off values [15].

Statistics

The normality of variables distribution was tested using Kolmogorov-Smirnov test. Results were described as mean and standard deviation (SD). Categorical variables were reported as frequencies. Differences between proportions were assessed with Pearson χ^2 test.

Body girths means obtained with the subject in both standing and supine positions were compared through Student's *t*-test for related samples. Differences in body girths means obtained in the two body positions according to BMI categories (normal weight or overweight/obesity) were compared using Student's *t*-test for independent samples.

Data set was divided into quartiles, according to the distribution of girth measurement values on both standing and supine positions. Association between girth measurements obtained in the two body positions was quantified by Intraclass Correlation Coefficient (ICC) [16]. Agreement between quartiles of girth measurements performed in both standing and supine positions was determined using the weighted kappa with the Fleiss classification [17] and also by the graphical method of Bland and Altman [18].

Statistical significance was set at $p < 0.05$. All analyses were conducted with the Software Package for Social Sciences (SPSS) for Windows (version 20.0; SPSS, Inc., Chicago, IL).

Results

Baseline characteristics of the 123 patients enrolled in the present study are displayed in Table 1, for the entire sample and stratified by age groups. Patients' mean age (SD) was 52.7 (15.7) years and 27.6% patients were aged ≥65 years. Younger patients (aged <65 years) presented higher education level, were more likely to be single and presented better nutrition status than patients aged ≥65 years. The highest proportion of patients was independent according to Katz index. Mean BMI was 26.8 (5.1) kg/m^2 and 57.7% patients presented overweight or obesity (BMI ≥25 kg/m^2).

Body girths mean values obtained in both standing and supine positions are presented in Table 2. Measurements obtained in standing position were systematically higher than measurements obtained in supine position (p ≤0.001). The highest difference (1.1 cm) was observed for hip girth. Nevertheless, all ICC values correspond to a strong correlation (ICC ≥0.97) [16]. Moreover, the agreement between measurements is high, ranging from 81.3% to 87% and all kappa values correspond to a good agreement (0.80-1.00) according to Fleiss classification [17]

Table 1 – Patients' baseline characteristics for the entire sample and according to age groups.

Characteristics	Entire sample (n=123)	< 65 years (n=89)	≥ 65 years (n=34)	*p*
Age (years), mean (SD)	52.7 (15.7)	45.5 (11.9)	71.3 (5.3)	<0.001[a]
Gender, n (%)				
Women	57 (46.3)	45 (50.6)	12 (35.3)	
Men	66 (53.7)	44 (49.4)	22 (64.7)	0.159[b]
Education (years), n (%)				
0-4	44 (35.8)	26 (29.2)	18 (53.0)	
5-12	64 (52.0)	51 (57.3)	13 (38.2)	0.049[b]
>12	15 (12.2)	12 (13.5)	3 (8.8)	
Marital status, n (%)				
Single	15 (12.2)	13 (14.6)	2 (5.9)	
Married	84 (68.3)	64 (71.9)	20 (58.8)	<0.001[b]
Widowed	15 (12.2)	11 (12.4)	4 (11.8)	
Divorced	9 (7.3)	1 (1.1)	8 (23.5)	

Table continued

Table 1 continued

Characteristics	Entire sample (n=123)	< 65 years (n=89)	≥ 65 years (n=34)	*p*
Katz index, n (%)				
Independent	120 (97.6)	88 (98.9)	32 (94.1)	
Moderate and severe dependence	3 (2.4)	1 (1.1)	2 (5.9)	0.185[b]
Nutritional status (NRS-2002), n (%)				
Normal	114 (92.7)	86 (96.6)	28 (82.4)	
Risk	9 (7.3)	3 (3.4)	6 (17.6)	0.013[b]
BMI (kg/m^2), mean (SD)	26.8 (5.1)	27.1 (5.4)	25.8 (3.9)	0.245[a]
BMI categories (kg/m^2), n (%)				
Normal weight	52 (42.3)	36 (40.4)	16 (47.1)	
Overweight and obesity	71 (57.7)	53 (59.6)	18 (52.9)	0.545[b]

SD: standard deviaton; BMI: body mass index; NRS-2002: Nutritional Risk Screening - 2002

[a] Independent samples *t*-Test

[b] Pearson Chi-square test

Table 2 – Comparison between body girths in standing and supine positions.

Girths (cm)	Standing, mean (SD)	Supine, mean (SD)	Difference[a] mean (95%CI)	p [b]	ICC	Weighted kappa[c]	Agreement (%)[c]
Arm	29.9 (4.3)	29.2 (4.1)	0.7 (0.6-0.9)	<0.001	0.97	0.87	83.7
Waist	93.2 (14.2)	92.6 (14.0)	0.6 (0.3-0.9)	0.001	0.99	0.89	86.7
Hip	99.9 (9.9)	98.8 (10.0)	1.1 (0.8-1.4)	<0.001	0.99	0.90	87.0
Calf	35.6 (3.5)	35.0 (3.5)	0.6 (0.5-0.8)	<0.001	0.97	0.84	81.3

SD: standard deviation; CI: confidence interval; ICC: intraclass correlation coefficient;

[a] Difference = Girth in standing position - Girth in supine position

[b] *Student's t-test* for related samples

[c] Data in quartiles according to sample distribution

Comparison between the differences in body girths obtained in the two body positions across two BMI categories (normal weight and overweight or obesity) are presented in Table 3. Mean differences in body girths measured in the two body positions did not significantly change between patients with normal weight and overweight or obese patients. Agreement, kappa and ICC values are also similar between the two BMI categories.

Table 3 – Body girths differences for standing and supine positions, comparison between normal weight (n=52) and overweight or obese (n=71) patients.

Girths (cm)	Standing / supine difference, normal weight mean (SD)	Standing / supine difference, overweight or obesity mean (SD)	Difference[a] mean (95% CI)	p [b]	Agreement (%)[c] normal weight (kappa)[d]	Agreement (%)[c] overweight or obesity (kappa)[d]	ICC normal weight	ICC overweight or obesity
Arm	0.6 (1.0)	0.8 (1.1)	-0.2 (-0.6-0.1)	0.147	86.5 (0.82)	83.1 (0.80)	0.92	0.97
Waist	0.2 (0.3)	0.9 (0.2)	-0.7 (-1.3-0.04)	0.063	86.5 (0.82)	88.0 (0.89)	0.95	0.99
Hip	1.2 (0.2)	1.1 (0.2)	0.1 (-0.4-0.6)	0.666	80.8 (0.74)	91.6 (0.91)	0.95	0.98
Calf	0.6 (0.1)	0.7 (0.1)	-0.1 (-0.4-0.1)	0.332	80.8 (0.72)	81.7 (0.81)	0.95	0.97

SD: standard deviation; CI: confidence interval; ICC: intraclass correlation coefficient

[a] Difference in positions for girths in normal weight - Difference in position for girths in overweight or obesity

[b] Student's *t*-test for independent samples

[c] Data in quartiles according to sample distribution

[d] Weighted kappa

Bland and Altman graphical representations (Figures 1 to 4) were displayed considering the effect of different BMI categories. For all body girths obtained in the two body positions it is possible to observe that body girth values are consistently higher for overweight or obese patients. There is little dispersion and observed differences are not dependent on the magnitude of the measurements for both normal weight and overweight patients. These representations corroborate graphically the high agreement found for measurements in the two body positions and the similarities between normal weight and overweight patients considering this agreement.

Further analysis was carried out in order to assess whether these results were different according to <65 years and ≥65 years age groups. Differences between body girths obtained in the two body positions were not statistically different when stratified by the two age categories, with exception for waist girth in patients aged ≥ 65 years (waist girth mean in standing position = 97.1 cm *versus* waist girth mean in supine position = 96.5 cm, p = 0.08) that almost reached the statistical significance. Regarding the comparison between normal weight and overweight or obesity, there was no change after stratification by age groups.

Figure 1 - Bland and Altman plot to arm girth (cm) obtained in the standing and supine positions and stratified by BMI categories.

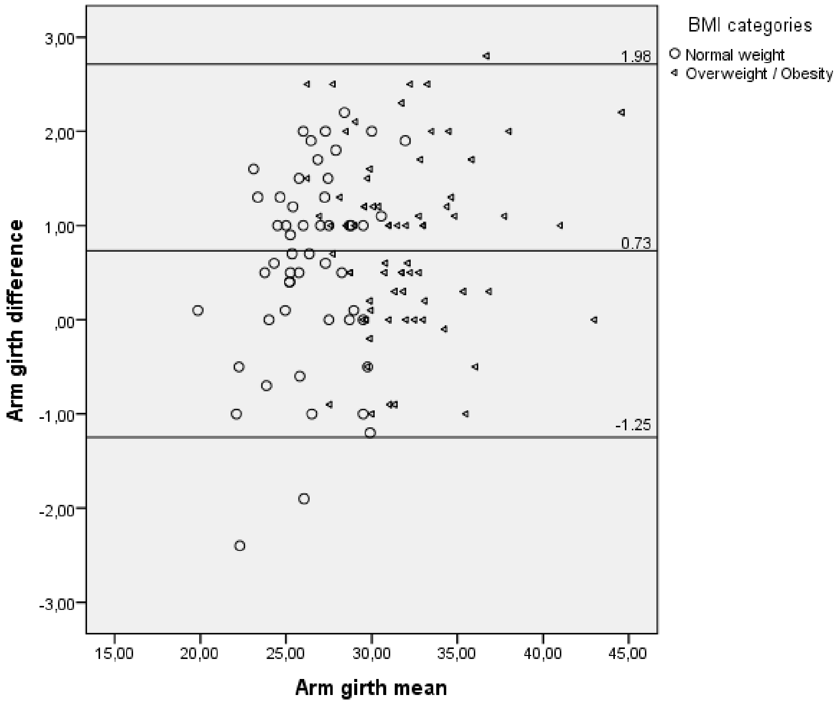


Figure 2 - Bland and Altman plot to waist girth (cm) obtained in the standing and supine positions and stratified by BMI categories.

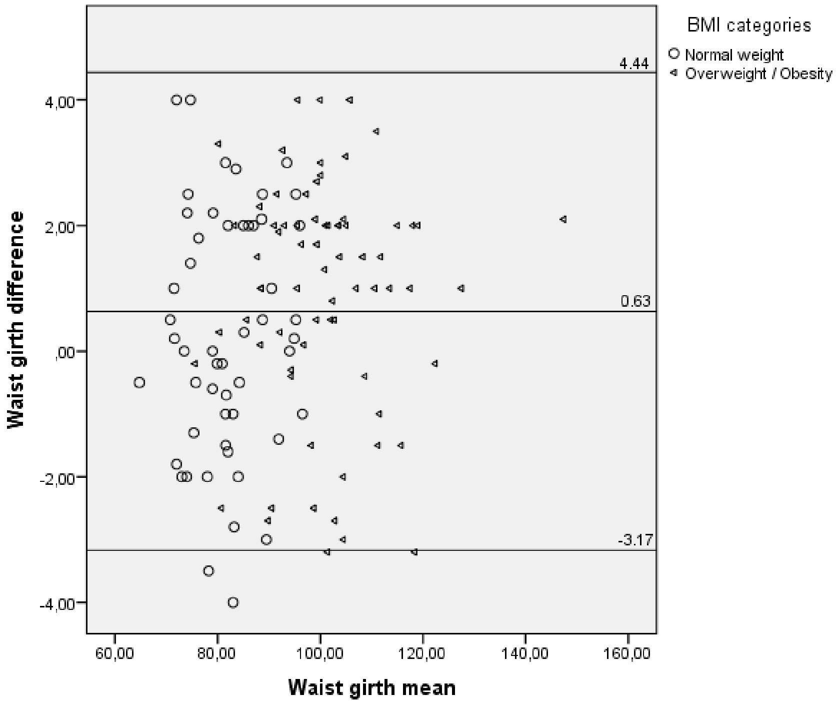


Figure 3 - Bland and Altman plot to hip girth (cm) obtained in the standing and supine positions and stratified by BMI categories.

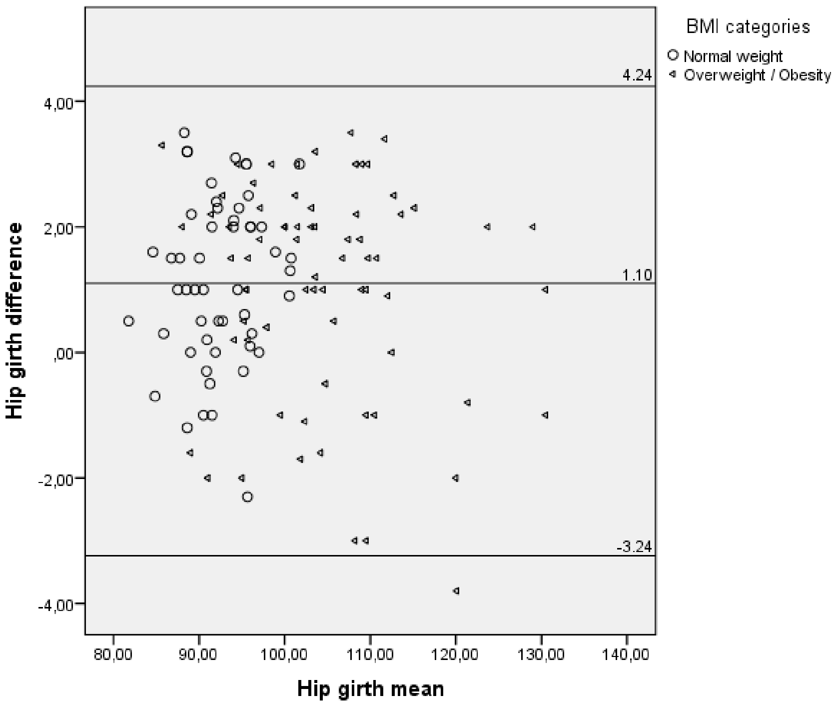
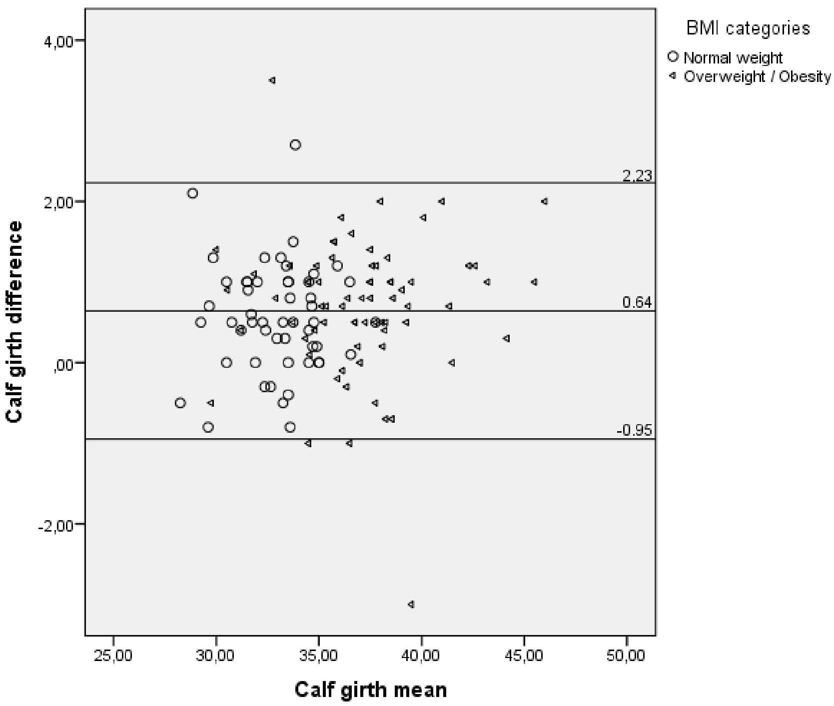


Figure 4 - Bland and Altman plot to calf girth (cm) obtained in the standing and supine positions and stratified by BMI categories.



Discussion

The present study results show there are little posture related differences in the assessment of body girths among hospitalized patients.

Our results corroborate previous findings concerning the effect of posture on body girths in older adults [7] and firstly report this effect among hospitalized younger patients. For patients aged ≥65 years, it is noteworthy that the absence of differences in waist girth measured in standing and supine positions is in accordance with a previous report [7], even though sample characteristics differ, *i.e.*, not all previous study participants were hospitalized and they were significantly older than in the present study (mean age of 77.3 years *versus* mean age of 71.3 years).

Considering the effect of BMI categories on body girths obtained in the two body positions, no significant differences were found between overweight or obese and normal weight patients. As far as we are concerned, there are no previous results to which compare these findings. These similarities reveal that, for a trained anthropometrist, body complexion does not appear to modify the differences between standing and supine positions. Thus, the assessment of arm, waist, hip or calf girths in an overweight or obese bedridden patient does not have a greater influence from body posture than the assessment of a patient with normal weight. These observations are substantiated by Bland and Altman graphical results.

Therefore, and in contrast to what was theoretically expected, body girths assessment of bedridden obese patients does not differ from the assessment of bedridden normal weight patients.

In the present analysis, BMI was used as a surrogate indicator of body complexion. Although it is well-recognized and universally used for clinical purpose, this index does not consider important variables for body composition assessment, other than weight and height [19]. Moreover, BMI is not the most accurate health status predictor, as demonstrated in a previous study [20] where, using waist girth results, for a given waist girth value, overweight or obese and normal weight individuals had comparable health risks.

Even though the main aim of this study was to explore the influence of a high BMI value compared to a normal BMI value, the exclusion of patients with a BMI of <18.5 Kg/m^2 could limit the external validity of present results for individuals in this condition. However, only five patients (4.1%) were excluded, thus, the hypothetical inclusion of those individuals was not likely to change the results obtained here.

In order to comply with the inclusion criteria, patients unable to change their body position were not included in the study. It remains to be documented if in bedridden patients body girths measurement could be more biased than in patients without mobility restraints, namely due to physical inactivity and muscle disuse.

Sample size allowed for detecting differences and patients in the present sample were from different hospital wards, which ensured variety of conditions and body composition patterns.

The present sample mean BMI (26.8 kg/m^2) corresponds to overweight classification and 57.7% patients were overweight or obese. Results could potentially be different if evaluated within populations with other BMI categories distribution.

Future research should explore this effect among other hospitalized patients and community-dwelling individuals, with higher and lower BMI and also, among other ethnic groups. In conclusion, body girths assessment in standing and supine positions in hospitalized adults and older adults differ. However, these differences are small and they are not dependent on BMI categories.

Conflicts of interest

The authors declare no conflicts of interest.

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Chapter II.b

Triceps skinfold compressibility in hospitalized patients – an exploratory analysis

Triceps skinfold compressibility in hospitalized patients – an exploratory analysis

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Key-words: anthropometry; nutritional assessment; compressibility; skinfold thickness.

Abstract

Background: Triceps skinfold (TSF) compressibility can introduce error on the measurement and its interpretation. However, it has not been explored yet in a clinical setting. Lipotool® is a digital calliper which acquires 60 measures per second and firstly allows the study of compressibility. Therefore, the present study aims to explore through an innovative technique, TSF compressibility and its associated factors among a sample of hospitalized patients.

Methods: A cross-sectional study was conducted among hospitalized adult patients. Evolution of tissue compressibility during two seconds was registered and 120 TSF values were obtained. Compressibility was determined according to time (τ) and according to the difference between the initial value and the final value (TSF difference). Multivariable linear regression models were performed in order to identify factors associated with TSF compressibility.

Results: 106 patients (30.2% aged ≥65 years) composed the study sample. Time of compressibility (τ) was no significantly associated with any of the studied variables, but compressibility based on TSF difference was independently associated with TSF thickness (regression coefficient (95% CI) = 0.38 (0.01-0.05), *p*= 0.002) and nutritional risk (regression coefficient (95% CI) = 0.23 (0.12-1.23), *p*= 0.018).

Conclusion: Among a sample of hospitalized patients, time of compressibility (τ) was not affected by any of the studied factors. However, undernutrition risk and the TSF thickness were factors independently associated with higher compressibility assessed by the difference between the initial and final TSF value.

Introduction

Skinfold thickness is often used for body composition assessment due the accessibility, the non-invasive features and the ability to measure subcutaneous adiposity [(1, 2)].

In skinfold thickness measurement with a skinfold calliper, a constant pressure is applied for a defined period of time [(3, 4)]. The tissue's dynamic response to this pressure is defined as compressibility [(1, 5)]. This characteristic has been studied by comparing skinfold calliper measurements and subcutaneous fat thickness assessed by coarse methods such as imaging methods, cadaver studies and empiric comparisons [(1, 5)].

There are underlying suppositions on the estimation from skinfold measurement: skin thickness is negligible, adipose tissue has constant characteristics and also that proportion of subcutaneous to visceral fat is equivalent in all subjects [(1)]. Notwithstanding this, it has been previously shown that compressibility varies according to the sites of measurement and between individuals, influencing the relation between the measurement and the actual adipose tissue thickness, introducing error in the estimation of body fatness [(1, 5)].

Gender [(5)], age [(6)], hydration status [(6)], skin thickness [(7)], subcutaneous tissue pressure [(7)] and site of measurement [(8)] have been previously described as factors associated with compressibility. Nevertheless, over the past few years, knowledge on compressibility has not significantly increased.

An integrated system, Lipotool®, was recently developed. This equipment consists of a digital skinfold calliper and a software application [9]. The system acquires 60 measurements per second [9]. Thus, this novel methodology firstly permits the study of dynamic tissue's response evolution during the measurement[9].

From all skinfold thickness sites, triceps skinfold (TSF) is the most used in clinical practice, as, along with mid-arm circumference, it integrates mid-arm muscle circumference formula, a simple method that allows for the estimation of muscle mass [10].

Regarding the wide use of TSF, the minimization of error is of utmost importance in order to provide an adequate use and interpretation for clinical practice. Nonetheless, as far as we are concerned, skinfolds compressibility has not been explored yet in a clinical setting. Therefore, the present study aims to explore through an innovative technique, TSF compressibility and its associated factors among a sample of hospitalized patients.

Materials and Methods

Study sample and design

A cross-sectional study was conducted in a general university hospital. Patients were eligible to participate in the study if they were aged 18 years and over, Caucasian, conscious, cooperative and able to provide written informed consent.

Critically ill patients, *i.e.*, with a life-threatening medical or surgical condition requiring intensive care unit level care, presenting severe organ system dysfunction and needing for active therapeutic support were excluded [11]. Pregnancy and patient ward isolation were also defined as exclusion criteria.

Ethics

This research was carried out according to the recommendations established by the Declaration of Helsinki and approved by the institutional ethics and review boards of *Centro Hospitalar do Porto*. All study participants provided a written informed consent.

Data collection

Demographical data were obtained by one trained registered nutritionist through a structured questionnaire within 72 hours of admission to hospital.

Education was evaluated by the number of completed school years and the following categories were created: 0-4, 5-12 and more than 12 years. Marital status was categorized as single, married or in a civil partnership, divorced and widowed. Independence in activities of daily living was assessed with the Katz index [12].

Patients' nutritional status was evaluated with Nutritional Risk Screening (NRS) 2002 [13]. Standing height (cm) was measured with a metal tape (Rosscraft, Innovations Incorporated, Surrey, Canada) with a 0.1 cm resolution and with a headboard. Body weight (kg) was assessed with a calibrated portable beam scale with 0.5 kg resolution.

Triceps skinfold thickness (mm) was obtained with Lipotool® digital calliper after performing the measurement during two seconds, as established by the protocol [3].

All measurements were performed by the same trained registered nutritionist. The intra- and inter- observer technical error of measurement was calculated for all measurements. Intra-observer ranged from 0.2% to 0.9%, and inter-observer error ranged from 0 to 6.6%. These values are considered acceptable for trained anthropometrists [14, 15].

Body mass index (BMI) was determined through the standard formula [weight (kg) / height^2 (m)] [16] and BMI categories were created according to the World Health Organization cut-offs [17].

Statistics

Results were described as mean and standard deviation (SD) or as median and interquartile range (IQR) according to normality of distribution, assessed with Kolmogorov - Smirnov test.

Data on TSF measurements were provided by Lipotool® software and the evolution of tissue compressibility during two seconds was registered, as this method acquires 60 measurements per second. Thus, in the end of the measurement, 120 values were obtained.

Therefore, compressibility was determined according to a method based on τ, *tau*, a measurement of time expressed in seconds, that reflects adipose tissue dynamic response to compression, being an individual characteristic. Thus, lower τ values mean that the skinfold compress faster, and, therefore, presents higher compressibility. τ value was obtained after computing the inverse of the exponent of a regression equation displayed for the 120 measurement sets of each patient.

Alternatively, another method was used to define compressibility. This method was based on the difference computed between the initial value and the final value, from the 120 TSF measurements acquired by the digital calliper. Thus, high difference between initial and final TSF value corresponds to high compressibility.

Data set was divided into tertiles of TSF, tertiles of τ and tertiles of difference between TSF initial and final value (TSF difference), according to the sample distribution. In order to select variables associated to compressibility, patients' baseline characteristics were compared across τ tertiles and TSF difference tertiles. Patients' baseline characteristics were also compared across TSF tertiles.

All the comparisons were computed by One-way ANOVA test if distribution was normal, or Kruskal-Wallis test, if non-normal distribution. Categorical variables were reported as frequencies. Differences between proportions were assessed with Pearson χ^2 test.

Furthermore, multivariable linear regression models were built in order to identify the independent variables associated with compressibility, assessed by τ or as TSF difference. The following variables were included in the models: TSF value (continuous), age (continuous), nutritional status (categorical) and gender (categorical), as these variables were considered as being potential confounders or covariates.

Statistical significance was set at $p < 0.05$. All analyses were conducted with MATLAB (MathWorks, Inc., Natick, MA) and the Software Package for Social Sciences (SPSS) for Windows (version 20.0; SPSS, Inc., Chicago, IL).

Results

Baseline characteristics of the 106 patients enrolled in the present study are displayed in Table 1, for the entire sample and stratified by TSF tertiles. Mean age (SD) was 53.1 (15.8) and 30.2% patients were aged ≥65 years. There were 56.6% overweight or obese patients and 11.3% patients were at undernutrition risk (Table 1). The highest and the lowest time of compressibility (τ) were observed for patients in the 2nd TSF tertile and in the 1st TSF tertile, respectively. The highest TSF difference was observed for patients in the 3rd TSF tertile (Table 1).

As shown in Table 2, patients' characteristics did not differ across τ tertiles, with exception for TSF difference, which was higher in the 2nd and 3rd τ tertiles than in the 1st τ tertile. Otherwise, BMI, TSF thickness and τ value increased from the 1st to the 3rd TSF difference tertiles (Table 3).

Table 1 – Patients' baseline characteristics for the entire sample and according to triceps skinfold tertiles.

	Entire sample (n=106)	1st ≤11.5 (n=35)	2nd 11.8-21.2 (n=34)	3rd ≥21.3 (n=37)	*p*
Age (years), mean (SD)	53.1 (15.8)	55.5 (15.7)	53.5 (13.8)	47.0 (16.9)	0.066[a]
Age categories (years), n (%)					
<65	74 (69.8)	23 (65.7)	23 (67.6)	28 (75.7)	
≥65	32 (30.2)	12 (34.3)	11 (32.4)	9 (24.3)	0.258[b]
Gender, n (%)					
Women	49 (46.2)	1 (2.9)	19 (55.9)	29 (78.4)	
Men	57 (53.8)	34 (97.1)	15 (44.1)	8 (21.6)	<0.001[b]
Education (years), n (%)					
0-4	41 (38.7)	9 (25.7)	17 (50.0)	15 (40.5)	
5-12	54 (50.9)	20 (57.1)	14 (41.2)	20 (54.1)	0.188[b]
>12	11 (10.4)	6 (17.1)	3 (8.8)	2 (5.4)	
Marital status, n (%)					
Single	15 (14.2)	6 (17.1)	3 (8.8)	6 (16.2)	
Married	72 (67.9)	23 (65.7)	25 (73.5)	24 (64.9)	0.310[b]
Widowed	12(11.3)	5 (14.3)	5 (14.7)	2 (5.4)	
Divorced	7 (6.6)	1 (2.9)	1 (2.9)	5 (13.5)	
Katz index, n (%)					
Independent	103 (97.2)	33 (94.3)	34 (100)	36 (97.3)	
Moderate and severe dependence	3 (2.8)	2 (5.7)	0 (0)	1 (2.7)	0.359[b]
Nutritional status (NRS-2002), n (%)					
Normal	94 (88.7)	28 (80.0)	30 (88.2)	36 (97.3)	
Risk	12 (11.3)	7 (20.0)	4 (11.8)	1 (2.7)	0.068[b]
BMI (kg/m^2), mean (SD)	26.2 (6.0)	22.6 (5.4)	26.1 (3.5)	29.7 (6.3)	<0.001[a]
BMI categories (kg/m^2), n (%)					
Underweight or normal weight	46 (43.4)	25 (71.4)	12 (35.3)	9 (24.3)	
Overweight or obesity	60 (56.6)	10 (28.6)	22 (64.7)	28 (75.7)	<0.001[b]
TSF (mm), mean (SD)	19.1 (12.1)	8.6 (2.0)	16.9 (2.9)	31.7 (11.1)	<0.001[a]
τ (s), median (IQR)	0.16 (0.16)	0.15 (0.13)	0.23 (0.14)	0.16 (0.11)	0.015[c]
TSF difference (mm)[d], median (IQR)	0.87 (1.02)	0.60 (0.98)	0.72 (0.94)	1.2 (1.3)	0.007[c]

TSF: triceps skinfold; SD: standard deviation; IQR: interquartile range; BMI: body mass index;
NRS-2002: Nutritional Risk Screening – 2002;
[a] One-way ANOVA;
[b] Pearson Chi-square test;
[c] Kruskal-Wallis test ;
[d] Triceps skinfold difference: Initial value - Final value, across a set of 120 measurements

Table 2 – Patients' baseline characteristics according to time of compressibility (τ) tertiles of sample distribution.

	1st ≤0.13 (n=35)	2nd 0.14-0.23 (n=35)	3rd ≥0.23 (n=36)	*p*
Age (years), mean (SD)	54.4 (14.6)	54.0 (15.6)	50.9 (17.4)	0.591[a]
Age categories (years), n (%)				
<65	23 (65.7)	24 (68.6)	27 (75.0)	
≥65	12 (34.3)	11 (31.4)	9 (25.0)	0.682[b]
Gender, n (%)				
Women	13 (37.1)	17 (48.6)	19 (52.8)	
Men	22 (62.9)	18 (51.4)	17 (47.2)	0.394[b]
Education (years), n (%)				
0-4	11 (31.4)	15 (42.9)	15 (41.7)	
5-12	19 (54.3)	16 (45.7)	19 (52.8)	0.669[b]
>12	5 (14.3)	4 (11.4)	2 (5.6)	
Marital status, n (%)				
Single	6 (17.1)	4 (11.4)	5 (13.9)	
Married	23 (65.7)	22 (62.9)	27 (75.0)	0.472[b]
Widowed	5 (14.3)	6 (17.1)	1 (2.8)	
Divorced	1 (2.9)	3 (8.6)	3 (8.3)	
Katz index, n (%)				
Independent	34 (97.1)	34 (97.1)	35 (97.2)	
Moderate and severe dependence	1 (2.9)	1 (2.9)	1 (2.8)	0.984[b]
Nutritional status (NRS-2002), n (%)				
Normal	28 (80.0)	34 (97.1)	32 (88.9)	
Risk	7 (20.0)	1 (2.9)	4 (11.1)	0.077[b]
BMI (kg/m^2), mean (SD)	25.9 (6.0)	26.3 (4.0)	26.3 (7.5)	0.952[a]
BMI categories (kg/m^2), n (%)				
Underweight or normal weight	16 (45.7)	15 (42.9)	15 (41.7)	
Overweight or obesity	19 (54.3)	20 (57.1)	21 (58.3)	0.940[b]
TSF (mm), mean (SD)	18.9 (13.6)	18.0 (9.2)	21.1 (13.0)	0.542[a]
τ (s), median (IQR)	0.09 (0.04)	0.16 (0.05)	0.33 (0.14)	<0.001[c]
TSF difference (mm)[d], median (IQR)	0.61 (1.0)	0.75 (1.1)	1.19 (1.2)	0.026[c]

TSF: triceps skinfold; SD: standard deviation; IQR: interquartile range; BMI: body mass index;
NRS-2002: Nutritional Risk Screening – 2002;
[a] One-way ANOVA;
[b] Pearson Chi-square test;
[c] Kruskall-Walis test;
[d] Triceps skinfold difference: Initial value - Final value, across a set of 120 measurements

Table 3 – Patients' baseline characteristics according to triceps skinfold difference [a] tertiles of sample distribution.

	1st ≤0.53 (n=34)	2nd 0.54-1.27 (n=36)	3rd ≥1.28 (n=36)	*p*
Age (years), mean (SD)	56.1 (14.3)	52.9 (17.2)	50.4 (15.7)	0.418[b]
Age categories (years), n (%)				
<65	23 (67.6)	24 (66.7)	27 (75.0)	
≥65	11 (32.4)	12 (33.3)	9 (25.0)	0.703[c]
Gender, n (%)				
Women	10 (29.4)	19 (52.8)	20 (55.6)	
Men	24 (70.6)	17 (47.2)	16 (44.4)	0.056[c]
Education (years), n (%)				
0-4	10 (29.4)	14 (38.9)	17 (47.2)	
5-12	19 (55.9)	20 (55.6)	15 (41.7)	0.434[c]
>12	5 (14.7)	2 (5.6)	4 (11.1)	
Marital status, n (%)				
Single	1 (2.9)	6 (16.7)	8 (22.2)	
Married	24 (70.6)	23 (63.9)	25 (69.4)	0.169[c]
Widowed	6 (17.6)	5 (13.9)	1 (2.8)	
Divorced	3 (8.8)	2 (5.6)	2 (5.6)	
Katz index, n (%)				
Independent	33 (97.1)	35 (97.2)	35 (97.2)	
Moderate and severe dependence	1 (2.9)	1 (2.8)	1 (2.8)	0.999[c]
Nutritional status (NRS-2002), n (%)				
Normal	31 (91.2)	33 (91.7)	30 (83.3)	
Risk	3 (8.8)	3 (8.3)	6 (16.7)	0.459[c]
BMI (kg/m^2), mean (SD)	24.9 (4.1)	26.6 (7.0)	26.9 (6.3)	<0.001[b]
BMI categories (kg/m^2), n (%)				
Underweight or normal weight	19 (55.9)	13 (36.1)	14 (38.9)	
Overweight or obesity	15 (44.1)	23 (63.9)	22 (61.1)	0.199[c]
TSF (mm), mean (SD)	14.2 (7.1)	20.6 (12.4)	22.8 (14.0)	<0.001[b]
τ (s), median (IQR)	0.13 (0.08)	0.20 (0.24)	0.21 (0.20)	0.002[d]
TSF difference (mm), median (IQR)	0.30 (0.18)	0.83 (0.44)	1.92 (1.6)	<0.001

TSF: triceps skinfold; SD: standard deviaton; IQR: interquartile range;BMI: body mass index;
NRS-2002: Nutritional Risk Screening – 2002;
[a]: Triceps skinfold difference:nitial value - Final value, across a set of 120 measurements;
[b] One-way ANOVA;
[c] Pearson Chi-square test;
[d] Kruskall-Walis test

Results from the multivariable linear regression models are presented in Table 4. As shown in Model 1, time of compressibility (τ) was not significantly associated with any of the included variables. In contrast, as displayed in Model 2, compressibility based on TSF difference was associated with TSF magnitude (regression coefficient=0.38 (0.01-0.05), *p*=0.002) and nutritional status (regression coefficient=0.23 (0.12-1.23), *p*=0.018), after adjusting for age and gender. Thus, presenting higher TSF value, *i.e.*, a thicker TSF, and being at risk of undernutrition are factors apparently related to an increase in the difference between TSF initial and final value, meaning that the skinfold was more compressed and, therefore, presents higher compressibility.

Table 4 – Multivariable linear regression models for prediction of triceps skinfold (TSF) compressibility.

	Regression coefficient (95% CI)	*p*
Model 1[a]		
TSF	0.03 (-0.01-0.01)	0.824
Gender (reference: women)	-0.06 (-0.37-0.21)	0.599
Age	-0.4 (-0.01-0.01)	0.695
Nutritional Status (NRS-2002; reference: normal)	0.16 (-0.71-0.08)	0.112
Model 2[b]		
TSF	0.38 (0.01-0.05)	0.002
Nutritional Status (NRS-2002; reference: normal)	0.23 (0.12-1.23)	0.018

CI: confidence interval; TSF: triceps skinfold thickness (mm); NRS-2002: Nutrition Risk Screening 2002

Variables included: age (years; continuous), nutrition status according to NRS-2002 (normal used as reference), gender (women used as reference) and TSF value (mm; continuous)

[a]:. Dependent variable: TSF compressibility defined as time (τ)

[b] Dependent variable: TSF compressibility computed as TSF initial value – TSF final value, across a set 120 measurements

Discussion

The present study results show that quantification of compressibility and its associated factors is dependent on the method used for describe this adipose tissue feature.

When compressibility was defined as time, *i.e.*, the time taken by the adipose tissue to respond to the pressure exerted by the calliper, differences were observed between TSF thickness tertiles, which could indicate that the skinfold magnitude was associated with compressibility. In addition, it is worth noticing that patients in the 2nd TSF tertile presented higher τ than patients in the 3rd TSF tertile. However, after performing a multivariable linear regression model, no independent association was found for any of the included variables, showing that, apparently, time of compressibility was not influenced by any of the studied factors.

In contrast, when compressibility was defined as the difference between initial and final TSF values obtained by the digital calliper, only BMI and time of compressibility differed between the tertiles of this variable. Nevertheless, after adjustment for potential confounders, such as gender and age, results from the multivariable linear regression model showed that undernutrition risk and the TSF magnitude were factors associated with an increase in compressibility, even though these associations were not strong, as demonstrated by the low regression coefficients obtained.

Explanations for these associations can be formulated, although only in a theoretical perspective as, with the present data, it is not possible to confirm them.

Therefore, a thicker TSF presents larger area of adipose tissue and this increase the potential of being compressed. Otherwise, an individual classified as being at risk of undernutrition is potentially likely to present more laxity in skin and adipose tissue, which can influence skinfolds compressibility towards higher values.

Transposing the present results for clinical practice, TSF thickness and undernutrition risk are characteristics susceptible of affecting the association between the actual value and the calliper reading, potentially introducing error by an increase in adipose tissue compressibility. Thus, by causing more compression in the skinfold, this error can lead to an underestimation of TSF thickness, *i.e.*, to a lower value reading, and, therefore, to a misinterpretation of the measurement.

Moreover, once τ indicates skinfolds compressibility, as time of response to a constant pressure, a higher time of response is expected to be associated to lower compressibility, as the tissues compress slowly. In contrast, a higher difference between the initial and final TSF value means that the tissue went through more compression, and is, therefore, associated with higher compressibility. Notwithstanding this, our results show that τ and TSF difference vary in the same direction, as τ values are higher in TSF difference 2nd and 3rd tertiles and TSF difference values are higher in the 2nd and 3rd tertiles of τ.

Considering the aforementioned methods for evaluating compressibility and the results actually obtained, there is an apparent counterintuitive observation. Nevertheless, it is worth noticing that these two methods are related with two different aspects of compressibility, time of response and the skinfold dimension. Thus, a skinfold that takes more time to be compressed and is, therefore, less compressible according to this definition, may simultaneously present a higher difference between the value in the beginning of the measurement and the value attained when the process is complete.

Although this novel methodology has been previously used in other settings [(18)], as far as we are concerned, this is the first report on the exploration of TSF compressibility as a quantifiable variable and its associated factors in a clinical setting. Consequently, there are no previous results to which compare our findings. Even though one approach detected consistent associations and the other one did not, they cannot be compared in terms of accuracy as these two methods assess different features.

Notwithstanding this, and in a clinical perspective, the absence of association with other factors found for compressibility defined as time is not sufficient to assume that there are no differences or even that compressibility did not affect measurements performed in the present sample. We can further hypothesize that, in the two seconds the measurement is performed, τ may be related to a more precocious moment of the process than the TSF difference. Thus, it is not known if in a larger period of measurement these results could be different.

Present results concern TSF only. As it has been already documented through results from studies [(5,8,19)] using different methodologies, adipose tissue compressibility varies according to the site of measurement. Thus, it is not known whether these results would be different if other skinfolds were evaluated.

In order to comply with the inclusion criteria, no critically ill or functionally impaired patients were enrolled. Moreover, the majority of the participants were independent in activities of daily living and there was a small proportion of patients at nutritional risk. Thus, the present sample can be considered homogenous and this feature may have influenced the results obtained. Therefore, it is not known if present results would be different in a wider sample of hospitalized patients or, even, among critically ill or bedridden patients.

In the future, it would be important to further explore compressibility through the present methodologies in other settings, such as in community-dwelling adults and older adults and different ethnic groups. The application of the present methods in different settings could allow for both testing their reproducibility and improving the techniques used.

In conclusion, among a sample of hospitalized patients, time of compressibility (τ) was not affected by any of the studied factors. However, undernutrition risk and the TSF thickness were factors independently associated with higher compressibility assessed by the difference between the initial and final TSF value. Although the present study is merely an exploratory attempt to describe compressibility and its effects, our results emphasize the need for further research in order to determine the most accurate method to quantify compressibility, to infer on the associated factors and to control its effect.

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General discussion

The present work intends to increase the existing knowledge on the burden and the diagnosis of sarcopenia in a clinical perspective. The results reveal a high frequency of sarcopenia amongst hospitalized patients, not only in older adults aged 65 years or over, but also in younger patients aged between 18 and 64 years. This importantly demonstrates that this condition is not merely a geriatric syndrome, as previously documented. Besides, the co-existence of sarcopenia with other conditions such as undernutrition and overweight or obesity corroborates the multifactorial nature of sarcopenia.

Several factors, such as male gender, age ≥65 years, dependence on activities of daily living, undernutrition and admission to a medical ward, were independently associated with a sarcopenia diagnosis. In a clinical setting, it would be relevant to further explore these associations and to recognize the modifiable factors, in order to act on the prevention of sarcopenia. In the present results, undernutrition is the only identified modifiable factor. This finding corroborates the major advantage of undernutrition prevention in the avoidance of co-morbidities and also emphasizes the importance of timely undernutrition risk screening in clinical settings.

It is also shown that sarcopenia is independently associated with longer length of hospital stay but, after stratification by age categories, this association was only identified for adult patients aged less than 65 years old. The absence of association of sarcopenia with LOS among older patients is in agreement with a previous report [9] and contradicts another report [7]. Nevertheless, as discussed before in Chapter I.b, the disparity between studies may be due to different methodologies and dissimilar sample characteristics, such as the existence of different diagnoses and, even, higher severity of co-morbidities in older patients.

In regards to the investigation on the financial burden of sarcopenia in the hospital setting, it is shown in the present work that this condition is independently associated with increased hospital costs, especially among younger patients. It is worth noticing that the association of sarcopenia and LOS is reflected in the financial impact of sarcopenia, as LOS is closely related to higher hospitalization costs.

Moreover, association of sarcopenia with LOS was found to be present only among hospitalized younger patients. Hospitalization costs, although shown to be associated with both age groups, presented a stronger association among hospitalized patients aged 18 to 64 years. These findings for LOS and hospitalization costs may be explained by the presence of different clinical characteristics between younger and older adult patients. The simultaneous presence of several co-morbidities in older patients could have diminished the strength of the association of sarcopenia with clinical outcomes, such as LOS. Consequently, the financial impact of sarcopenia is also lower in older patients than in younger patients.

Notwithstanding this, it is important to consider the limitation related to the use of DRG codes. This system has been shown to underestimate the real hospitalization costs as it reflects only direct hospitalization costs and does not take into account indirect costs, as societal costs [(96)]. Nevertheless, this methodology was used in the present study as it allows for an assortment of patients with a diversity of diagnoses and procedures. Therefore, the present work provides an original and a broader perspective on the consequences that sarcopenia entails in a hospital setting.

As previously mentioned in this thesis, the simultaneous presence of sarcopenia with other conditions, such as overweight or obesity, was also assessed and explored. Therefore, besides the associations found for sarcopenia, sarcopenic overweight (or obesity) was by itself independently associated with longer LOS and increased hospitalizations costs when patients in those conditions were compared to non-sarcopenic patients.

Overweight sarcopenic patients had shorter hospitalizations compared to non-overweight sarcopenic patients. This was an unexpected finding. Although there is no previous information to which to compare this observation, it importantly reveals that overweight and obesity could have a protective effect in sarcopenic patients during the hospitalization process. This protective effect associated with overweight and obesity complies with previous evidence on the "obesity paradox". This phenomenon has been observed in a range of cardiovascular disease pathologies where overweight and obese patients paradoxically present better outcomes than normal weight or underweight patients [(97-99)]. A possible explanation for this counterintuitive finding is the protective role of overweight once a disease takes hold, as it increases the individual's chance to cope with treatment and with the adverse consequences.

Considering the present work findings directly related to sarcopenia, it is of major importance to address a few concerns.

Firstly, the cut-offs from European Consensus [(3)] used in the diagnosis of sarcopenia were created for older individuals and in the present work they were applied to younger adult patients, as there are no age-specific recommended cut-offs values available in literature. Thus, this may have caused an underestimation of sarcopenia frequency.

In addition, BIA was used to assess muscle mass. Although this technique is recommended by the EWGSOP [3], there are a number of inherent limitations to its use in the clinical practice, such as the lack of reliability in the assessment of patients with conditions like heart failure, kidney failure, and dehydration [52]. The non-exclusion of all patients with these conditions may have introduced a misclassification of muscle mass, and, subsequently, some sarcopenic patients may have not been identified. This may have led to an underestimation of sarcopenia frequency.

Furthermore, the diagnostic criterion of sarcopenia requires the performance of functional tests, which leads to the exclusion of critically ill patients and individuals with functional impairment. As these individuals are potentially the most susceptible to present sarcopenia, this is an important limitation of the current definition of this condition. In the present work, this restriction in the participants may limit the comparison between studies in regards to critical patients, making the present results impossible to generalize for those individuals.

This concern was already addressed in a recent study by Cerri *et al.*[9] carried out within a sample of 103 hospitalized elderly patients. These authors reported a prevalence of sarcopenia of 21.4% but noticed the inability of EWGSOP criteria to be satisfactorily applied in 22.3% patients who were not able to perform gait speed test and/or handgrip strength due to an acute physically disabling illness.

Even though the EWGSOP Consensus lists and recommends the most suitable techniques and cut-offs, the lack of standardization of diagnostic criteria leads to difficulties in comparing different studies [6]. Present results show that the frequency of sarcopenia is strongly dependent on the technique used for estimate muscle mass. Moreover, anthropometric measures are not recommended due to higher susceptibility to error [3]. As expounded in Chapter I.a, muscle mass estimated through mid-arm muscle circumference was associated with a considerably lower frequency of sarcopenia than with muscle mass assessed by BIA, which corroborates this EWGSOP position in regards to anthropometric measures.

Notwithstanding the limitations concerning the use of anthropometric measures for sarcopenia diagnosis, and as described in a previous section of this report, body girths and skinfold thickness, are still valuable resources for use in other purposes of clinical practice, due to their financial and accessible features.

Another aim of this work was to assess the effect of possible sources of error on body girths and triceps skinfold thickness, mainly because arm circumference and triceps skinfold thickness are included in mid-arm muscle circumference formula. It allows for the estimation of muscle mass and, subsequently, can be used in the diagnosis of sarcopenia. Thus, exploring potential sources of error could lead to the recognition and also to provide clues in order to minimize anthropometric measurement bias, consequently, developing and improving the anthropometric methodology of sarcopenia diagnosis.

In regards to body girths, it was initially hypothesised that body posture and body complexion, defined by BMI, could influence body girths measurement. The results show that, although existent, in adults and older adults, posture related differences are small and individual body complexion does not affect the differences observed between the measurements obtained in the two body positions.

Concerning triceps skinfold assessment, the present work used an innovative technique to objectively document and quantify compressibility, which has been considered a potential source of error by affecting the relationship between the skinfold thickness measured by the calliper and the actual skinfold thickness value [90]. Regarding skinfolds compressibility defined as time of compressibility, τ, *tau*, and after exploring possible factors associated with this characteristic, there was a lack of association between the studied variables. In contrast, when compressibility was inferred from the difference between initial and final TSF values, nutrition status and triceps skinfold values were found to be independently associated with higher compressibility, showing that compressibility could increase according to nutrition status and the magnitude of triceps skinfold measurement. This discrepancy demonstrates a need to further explore these methodologies in order to identify and control the effects of compressibility on TSF assessment.

Considering the development of the method based on anthropometric measurements that leads to sarcopenia diagnosis, the present work brought to light a number of issues. The recognition of small posture and physical complexion related errors associated to body girths assessment and the advancement in the possibility to quantify skinfolds compressibility, are potentially useful insights concerning the use of anthropometric measures. Nonetheless, further work should document if the theoretical control for the explored sources of error could increase the validity of those measurements.

Future perspectives

Regarding the techniques involved in sarcopenia diagnosis, besides comparing BIA with anthropometric measures, the comparison of sarcopenia diagnosis by BIA with those obtained with more precise methods such as DXA, CT and MRI, will further reveal differences in the frequency of sarcopenia. However, this analysis was not performed in the present work. In the future, it could be revealing to explore those comparisons between the aforementioned methods in order to further validate the use of BIA for sarcopenia diagnosis purpose.

Considering the issues the present reports addressed, the development of cut-offs specific for sarcopenia diagnosis in younger individuals is a relevant stage to reach. Moreover, it would be important to propose new specific cut-offs for the estimation of muscle mass based on anthropometric measures, taking into account the acquired knowledge on body circumferences. Besides, the possibility to determine skinfolds compressibility may allow for the development of corrected measurement protocols.

It would also be important to explore factors associated to skinfolds compressibility extending the analyses to other skinfolds, such as biceps, subscapular and iliac crest, that are also often used for body composition assessment purpose, and to improve the validity of the current technique used to determine compressibility.

The significant limitation concerning the exclusion of critically ill and functionally impaired patients the current definition of sarcopenia demands, should be further explored. It would be advantageous to improve the current diagnostic criteria of sarcopenia towards the inclusion of those patients.

In the future, it will be of utmost importance to carry on the effort on the development of the most suitable method for the diagnosis of sarcopenia and to reach a universal consensus in order to improve the comparison between studies, a crucial condition to the progress of investigation. Moreover, it would be also important that all sarcopenic patients were suitable to be identified, not only the individuals who are able to comply with the current diagnostic criteria.

Conclusions

Conclusions

The present work leads to the following overall conclusions:

In regards to sarcopenia burden among hospitalized patients:

1. Sarcopenia is frequent among hospitalized patients and this frequency varies widely depending on the applied diagnostic criteria. Sarcopenia was identified in a considerable proportion of adult patients between 18 and 64 years and in those who were non-undernourished, namely among overweight and obese.
2. Being male, aged ≥65 years, being dependent, being undernourished and being admitted to a medical ward were factors identified as being associated with sarcopenia among hospitalized adult patients. Sarcopenia is independently associated with longer LOS, although this association is stronger for patients aged 18 to 64 years. Moreover, sarcopenic overweight was associated with a higher probability of discharge home than non-overweight sarcopenia.
3. Sarcopenia is independently associated with hospitalization costs, increasing costs in 52.7% (58.5% for patients aged < 65 years and 34% for patients aged ≥ 65 years).

Concerning anthropometric measures and its feasibility for clinical practice:

1. Body girths assessment in standing and supine positions in hospitalized adults and older adults differ. However, these differences are small and they are not dependent on BMI categories.
2. Among a sample of hospitalized patients, time of compressibility (τ) was not affected by any of the studied factors. However, undernutrition risk and the TSF thickness were factors independently associated with higher compressibility assessed by the difference between the initial and final TSF value. Although this is an exploratory attempt to describe compressibility and its effects, our results emphasize the need for further research in order to determine the most accurate method to quantify compressibility, to infer on the associated factors and to control its effect.

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